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DIVISION OF RESEARCH SERVICES FY 1977 ANNUAL REPORT

National Institutes of Health
Bethesda, Maryland 20014

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DIVISION OF RESEARCH SERVICES

Report of Program Activities
July 1, 1976, through September 30, 1977

CONTENTS

	Page
Division of Research Services	1
Biomedical Engineering and Instrumentation Branch	9
Indivisudal Project Reports	
1. Pharmacokinetics	23
2. Implant Device Development	27
3. Trace Element Analysis in Biological Materials	29
4. The Role of Fluid Dynamics and Mass Transfer in Development of Atherosclerosis	32
5. Particulate Hydrodynamics in Porous Membranes	35
6. Instrumentation for Flow-Through Hollow Fiber Cell Culture Studies	38
7. Fiber Optic pH Probe	41
8. Electrical Safety Program for Clinical Center Patients and Patient Care Areas	43
9. Investigation of Oxidation Metabolism and Potassium Kinetics in the Cat Brain	45
10. Two-Dimensional Ultrasonic Imaging System	48
11. ELISA Reader	51
12. Blood Gas Analysis Data Acquisition System	53
13. Microprocessor-Based Biomedical Instrumentation	55
14. Development of Whole Body Hyperthermia Instrumentation and Control System	57
15. Development of Miniature Catheters for Clinical Use	59
16. Development of an In Vivo Micro Spectrophotofluorometer for Use in Laboratory Animals	61
17. Differential ph/Thermal Titration Apparatus	63
18. An Analytical Model for the Structural Response of Intracranial Contents to Systemic Arterial Pressure	65
19. Modulation of Transendothelial Mass Transport by Hydrodynamically Induced Steady and Unsteady Wall Shear Stress	67
20. Effects of Mechanical Stress on Proliferation and Morphological Development of Bone Cells in Culture	69
21. Multimode Visual Display	71
Environmental Health ans Safety Program	73
Environmental Safety Branch	74
Radiation Safety Branch	86
Library Branch	95

Page

Medical Arts & Photography Branch 101

Veterinary Resources Branch 105

Individual Project Reports

1. Animal Model Development 118
2. Development of Diets for Laboratory Animals 120
3. Tyzzer's Disease 122
4. Environmental Toxicosis of Rhesus Monkeys -- Perrine Primate Facility 124
5. Neoplasia in the Nude Mouse 126
6. Sodium Cyanate Neurotoxicity in Macaca nemastrina primates 128
7. Erythrocebus patas Monkey as an Animal Model for Cardiovascular Research 130
8. Effect of Season on Pituitary and Gnodal Hormone Levels in Adult Male Macaques. 132
9. Hormone Level During the Postpartum Interval in Nursing and Non-nursing Macaques 134
10. Mycoplasma-Induced Caprine Keratoconjunctivitis 136
11. Evaluation of Efficacy of M. Bovis PPD Tuberculin in the Detection of Tuberculosis in Wild Caught Indian Macaca mulatta Monkeys 138
12. Defining the Nude Mouse Model 141
13. Characterization of a New Viral Disease of Rabbits . . . 143
14. Experimental Atherosclerosis in Miniature Swine 145
15. The Pathogenesis of Chondrodysplasia in the Alaskan Malamute 147
16. Aging Studies on HSR, HSR-Stroke Prone, WKY Rats 149
17. In utero, Injection of Herpes Saimiri, Epstein-Barr Virus, or Guinea Pig-like Herpes virus in Pregnant Guinea Pigs 151
18. Evaluation of Therapeutic Effects of Iron-Dextran, Vitamin B_{12} and Folic Acid in Combating Experimentally Inducted Anemia in Rhesus Monkey (Macaca mulatta) . . . 153
19. Skeletal Age Development in Macaca mulatta 155
20. Nonhuman Primate Dietary Fiber Level Study 157
21. Anthelmintic Affect on Antibody Levels Following Primary and Secondary Immune Stimulation 159
22. Evaluation of a Purified Diet for Rodents 161
23. Establishment of a Pasteurella multocida-free Rabbit Colony by Use of Chemotherapy and Mass Air Movement 163
24. Effect of DDVP on Reproductive Performance, Weight Gain, and Immunologic Function in Four Strains of Mice . 165
25. Effect of Piperazine on T cell and B cell Function in Mice 167

NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES -- DR. JOE R. HELD, DIRECTOR

Report of Program Activities
July 1, 1976, through September 30, 1977

A. Objectives

The Division of Research Services supports intramural biomedical research conducted by the Bureaus, Institutes, and Divisions of the National Institutes of Health. The staff of professional and technical personnel meets the unique requirements of NIH research investigators and, in addition, carries out independent research to provide needed products and services. Division programs are organized into five functional areas: Biomedical Engineering and Instrumentation, Environmental Health and Safety, Library, Medical Arts and Photography, and Veterinary Resources.

B. Current Programs

Division programs offer a broad range of products and services. They include

1. Application of engineering principles and techniques to biomedical problems
2. Design, fabrication, and maintenance of special research instruments
3. Environmental surveillance to detect and eliminate conditions that impede high-quality research or create hazards for patients, employees, or the community
4. Surveillance of biohazards, control of radioactive materials, and maintenance of health and safety programs
5. Library and bibliographic services
6. Foreign language translation
7. Still photography and motion picture production
8. Graphic arts services and design of exhibits
9. Medical illustration and model making
10. Animal production, procurement, conditioning, and holding
11. Animal health services
12. Experimental surgery and related activities

13. Production of tissue cultures, microbiologic media, and biological preparations such as normal and immune sera required for research

14. Central processing and sterile preparation of laboratory glassware

C. Program Progress and Accomplishments

1. Biomedical Engineering and Instrumentation Branch

The technical problems presented to BEIB engineers become increasingly complex and challenging. Broad and intensive collaboration with biological scientists is required to translate the biological problem into technical criteria, design the necessary materials and methods, and verify that the technical performance is appropriate to the biological objective.

A number of novel chemical analytical procedures were refined this year. Advances in instrumentation and models for evaluating biologically relevant physical properties have also been made.

Principles of chemical engineering continue to be applied to pharmacokinetics, for example, in studies that trace the distribution of hazardous agents in vivo and in the environment. Improvements have been made in the methodology of hollow fiber cell culture to permit measurement of changes in oxygen consumption that indicate cellular response to pharmacological agents. The same technological base has been used to develop a versatile family of tissue/organ life support systems. Mathematical models are being developed to describe passive membrane transport through pores and gap junctions and to provide physical explanations for phenomena such as hindered diffusion. Mechanical devices are being designed to permit studies of visual tracking in humans and to investigate visual-vestibular interactions.

Noteworthy progress has been made in understanding the interaction of polymers used in implants with their physiological environment. Important improvements were made in the real-time mechanical ultrasound scanner. The scanner has proved to be highly effective in several types of ocular, cardiac, and abdominal procedures.

The Rental Program expanded by about 40 percent in number of rental contracts and about 25 percent in equipment utilization rate. Efforts are being made to enlarge the inventory of devices most commonly required by NIH investigators.

2. Environmental Health and Safety Program

a. Environmental Safety Branch

The staff of the Environmental Safety Branch (ESB) fulfilled numerous assignments related to research involving recombinant DNA molecules. Some of the tasks were undertaken to satisfy NIH intramural safety requirements, others were imposed by requirements of federal legislation, and still others entailed consultation with international organizations.

Also, two staff members were assigned on a full-time basis to supervise construction and certification of two maximum containment laboratories--one at NIH and the other at the Frederick Cancer Research Center.

ESB took part in two international biohazard control programs. It planned and sponsored the WHO/NIH Consultations on Facilitation and Safety in International Transfer of Research Materials held in Geneva, Switzerland, which instituted the WHO program on Safety in Microbiology, and contributed to the NIH/EMBO (European Molecular Biology Organization) Consultations on Laboratory Design in London, England, which resolved design discrepancies between the U.S. and European nations.

To control laboratory use of chemical carcinogens, ESB is working with other governmental organizations and professional societies to develop operational guidelines and design standards. Work began on compiling an ongoing inventory of chemical carcinogens in use at NIH. Procedures were established to govern the disposal of chemical carcinogens and toxic chemicals at NIH. A research project is underway to improve methods for disposal of the waste chemicals.

Staff additions have permitted an increase in accident investigation activities. A planning and evaluation team has been organized to develop and carry out a safety inspection program for NIH work places. The Department of Health, Education, and Welfare audited the NIH program and identified a few areas for improvement. The suggestions are receiving current attention.

Training efforts focused mainly on the development of educational materials and manuals, including four slide/cassette programs, Chemical Hazard Data Bulletins, the Environmental Health and Safety Report, a new series of safety posters, a chemical safety guide, and a compressed and liquified gases program and guide. A contract was initiated for the preparation of a programmed instruction course in "Fundamentals of Laboratory Safety." Training in biohazard control was given to 124 investigators, and two series of courses in chemical safety practices were offered to NIH investigators.

Continuing Branch programs which required considerable attention included collection and disposal of solid wastes, provision of high-purity water, and media production.

b. Radiation Safety Branch

The U.S. Nuclear Regulatory Commission conducted two inspections of NIH activities during the reporting period. The inspectors were pleased with improvements in the NIH radiation safety program and on numerous occasions have referred other licensees to NIH for technical assistance, particularly in the area of controlling hazards associated with the use of radioactive iodine. As a result of previous recommendations by the NRC, a program for renewal of radionclide authorizations was implemented. All authorizations now expire after three years, and reapplication and

attendance at a review training session is required for renewal. In conjunction with this program, 601 applications were reviewed and forwarded to the Radiation Committee for approval.

Initial training for NIH employees who work with radionuclides includes a two-week course, "Radiological Health for Radionuclide Users"; the course was given twice this year. Thirteen sessions were held of a second course, "Radiation Safety in the Laboratory," which is required of workers who use radionuclides but do not fall into the Authorized User category.

Technical assistance was provided to several hospitals, universities, federal agencies, commercial firms, former NIH employees, and concerned citizens regarding radiation safety. Most of the private citizen inquiries were in regard to medical and dental use of x-rays. The other requests for assistance were primarily in regard to the control of hazards from the use of radioiodine; several were referred to NIH by the NRC.

A total of 14,913 shipments of radioactive materials, with a combined activity of 231.5 curies, was received over the reporting period. The adjusted annual rates of increase were 17 and 23 percent, respectively. The Radiation Safety Branch (RSB) prepared 253 packages of radioactive materials for shipment from NIH investigators to authorized recipients.

The major portion of the radioactive waste pickup, processing, packaging, and disposal activities was contracted on January 3, 1977. During the reporting period, 83,632 trays of liquid scintillation vials, each containing 100 vials, were collected for packaging and burial. A total of 760 fifty-five gallon drums of compacted radioactive solid waste and solidified liquid waste was packaged for disposal by burial. A set of computer programs was written to handle radioactive waste counting and waste inventory records, which will enable RSB to maintain more up-to-date and accurate waste disposal records.

Laboratory surveillance and personnel monitoring steadily increased. A total of 3,571 radiation surveys of laboratories using radioactive materials was conducted. Approximately two-thirds of the surveys were conducted by contract and the remainder by RSB personnel. The number of NIH employees monitored monthly to assess exposure to radioactive materials increased from 2,127 at the beginning of last year to 2,532, a 19 percent increase.

3. Library Branch

An Automated Circulation Control System for monographs has increased effectiveness of services with regard to loans and processing of overdue materials. Bar coding of new journal issues as received and of bound volumes returned from the binder constitutes a head start toward preparation of the journal collection for inclusion in the automated system.

A major long-term Monograph Weeding Project was initiated to remove old, unused and unneeded books from the Library's collection. Each monograph on

the shelves is examined for retention in the Library's collection in accordance with the Library's Cope and Coverage Policy and guidelines approved by the Library Advisory Committee. Coordinated with the Weeding Project is the ongoing, but now intensified, program of selecting the latest research-level publications for addition to the collection as stipulated by the Library's Scope and Coverage Policy.

A printer attachment to the Ohio College Library Center (OCLC) terminal provides copy of on-line data used by librarians and library technicians in cataloging new acquisitions, which improves technical services.

The Library presented exhibits to observe National Black History Week and National Library Week; to honor Dr. Charles Richard Drew, father of the Blood Bank, and Dr. D. Carleton Gajdusek, NINCDS, 1976 Nobel Prize corecipient in Medicine; and to illustrate services provided by the Library and other Branches of the Division.

4. Medical Arts and Photography Branch

During the reporting period, technological improvements in the areas of photomicrography, photomacrography and photographic laboratory services were instituted. The progress was achieved by formal technical training and attendance at seminars and professional meetings as well as by replacing old equipment with advanced photographic equipment. There was an increased production of ten percent in design graphics, and the high level of quality work was maintained with no additions in personnel. In-house productivity efforts were augmented by more frequent utilization of outside contract services from private businesses in the Washington, D.C., area to keep pace with the ever mounting demands for services.

5. Veterinary Resources Branch

Procurement of rodents and rabbits increased considerably from 150,000 last year to 235,000 in 1977. Utilization of dogs by NIH investigators continues to decline. Only 360 foxhounds were procured in 1977, versus over 700 in 1976.

In-house animal production is limited to animals that are not available commercially or cannot be procured with quantity and quality guaranteed. In addition to 515,000 rodents and rabbits, small numbers of purebred foxhounds, rhesus monkeys, goats, burros, and miniature swine were produced by the Veterinary Resources Branch (VRB) during the reporting period. Production of biologics included blood or serum from a number of species of ungulates and 3,600 units of canine blood from the universal donor foxhound colony.

Nonhuman primates, cats, ungulates, and feral animals were purchased and conditioned. Although not well defined genetically or microbiologically and of lower quality than NIH-bred animals, they are satisfactory for certain studies. The animals are quarantined before being used in research programs and, during the quarantine period, given appropriate immunizations,

tested for a variety of infectious agents, and treated medically as required.

Services and collaborative support to NIH investigators were increased in several areas such as gnotobiotics, animal holding, and genetic monitoring of inbred strains of rodents. Major research contributions were made in development of a number of new animal models for human diseases. Additional "markers" to aid in establishing genetic profiles of inbred mice were developed, and efforts were continued to prevent or control a number of diseases in laboratory animals that interfere with their use as research tools. Research in nutrition led to development of open formula rations for all of our rodent colonies, improving reproduction performance and decreasing cost.

In addition to supplying animals for intramural investigators, breeding nuclei from the VRB genetic resource were provided to the international biomedical research community as part of our responsibilities as a WHO resource. About 240 investigators at 200 institutions were provided 5,565 animals to start breeding colonies.

All major small animal contract programs at the National Cancer Institute are now relying on VRB as the genetic base for their colonies. Germfree and pathogen-free animals were provided as pedigreed breeding nuclei for the Frederick Cancer Research Center and other contractors.

D. Division Management

1. Personnel Appointments

Mr. Newell Quinton and Mrs. Brenda Watts were appointed Administrative Officer and Equal Employment Opportunity Officer, respectively. The Management Analysis Office was expanded with the appointments of Mr. Dennis Burns as Systems Analyst, Mr. Wallace Carr as Industrial Engineer, and Mr. Dan Lewis as Management Analyst.

2. Personnel Management

Staffing and placement activities involved new initiatives in the area of cooperative education. Students from George Washington University and Montgomery College were hired as safety and biomedical technicians. For the first time, DRS participated in the NIH Visiting Program by providing an opportunity for visiting scientists to work in the Biomedical Engineering and Instrumentation Branch.

Classification issues created considerable concern. Several Branches were completely audited as a result of the Department of Health, Education, and Welfare three-year classification review. Controversy about pay category determinations continued in the Biomedical Engineering and Instrumentation Branch for certain groups of technicians.

In the area of employee development, the DRS Management Circular on Training Policy and Procedures was issued, delineating policy for all employee training participation. Participation in executive and general supervisory

programs continued at a good pace. In other areas, a total of 27 DRS employees attended Upward Mobility College; two were commended for maintaining at least a 3.0 grade point average. Also, 11 persons enrolled or continued with the Adult Education program, approximately 40 employees took part in a mini-seminar on "How to Apply for a Job," and 22 students took advantage of course offerings designed specifically for summer students.

A project was completed for the Executive and Management Development Branch which compiled the amount of supervisory training accrued by each supervisor. Once computerized, the information will be used to assist in developmental counseling.

3. Program Planning and Review

The Division's participation for the first time in the NIH Forward Plan offered an opportunity to present numerous policy and organizational issues to the Director and his staff in an orderly, comprehensive manner. Benefits are anticipated in improved budget submissions, better policy formulation and an enhanced understanding of the essential services that the Division provides to the NIH community.

Program reviews by Branch officials were based on input-output analyses at the section level. In addition to current assessments, efforts were made to relate investments of manpower and dollars to quantitative output measurements. The approach furnishes an improved basis for future program evaluations, benefit analyses, and effectiveness studies.

4. Evaluation Planning

Submission of five proposals for set-aside funding climaxed the Division's evaluation program. Proposals generally reflected the need for information to assess program policies and the related effects on research support programs. Proposals for set-aside funding included:

- Evaluation of Research Guidelines in NIH Extramural Programs
- Chemical Destructor Evaluation
- Evaluation of Centralized Analytical Instrumentation Facilities

5. General Administration and Budget

The concept of Zero Base Budgeting was introduced in program management. The process was presented from a decision-making standpoint, interrelating the FY 79 Forward Plan, workload manpower data and budget requests. Resources were allocated on the basis of program priority.

6. Management Analysis Projects

Analytical support to the Division included a comprehensive study of the Small Animal Section for computer applications, a study to convert the NIH Library from Management Fund to Revolving Fund, the development of a management information system for radiation safety activities, and a computerized record system for the equipment rental program. A pricing and

rate structure was developed for the future conversion of design graphics services to the Service and Supply Fund.

7. Equal Employment Opportunity

DRS representatives were selected to serve on the NIH Women's Advisory Committee and the Review Panel for the Study of Employee Conflict. Both representatives are ex officio members of the Division Human Relations Committee and will represent the concerns of women to management and employee organizations.

A new counselor for DRS was appointed to fill an existing vacancy. This appointee is located at the NIH Animal Center and is a member of the Division Human Relations Committee. An EEO questionnaire was devised to assess the concerns of employees regarding EEO and to provide input into the Affirmative Action Plan and the Federal Women's Program.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1976, through September 30, 1977

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH Dr. Murray Eden, Chief

I. SUMMARY

Continuing the trend of recent years, there is a growing awareness among NIH scientists of the capabilities of the professional staff of the Biomedical Engineering and Instrumentation Branch with respect to modern developments in engineering science, applied physics and mathematics. As a consequence, the technical problems presented to BEIB engineers tend to become more complex and challenging. We have met the challenge by broad and intensive collaboration with biological scientists to convert the demands of the biological problem into technical criteria, carry the design to practical realization and verify that the technical performance satisfies the biological objective. To accomplish these goals, we have organized informal project teams including several engineering or physical science specialists.

The range of our projects spans NIH research interests. Most projects involve development or refinement of instruments intended to measure, observe or describe in some analytic or quantitative way in vitro or in vivo biological systems. The systems we have helped to study represent virtually every level of organization: biochemical, cellular, organ or tissue, and holistic.

This year BEIB staff worked on the retirement of a number of novel chemical analytical procedures: trace elements such as platinum, magnesium, calcium and iron in tissue and fluids were assayed by improved flameless atomic absorption spectrophotometry and neutron activation analysis; chemical transformations--especially those involving hydronium production or incorporation--were measured by determining heats of reaction with a novel microcalorimeter; hemoglobin-oxygen association curves can now be determined automatically with the aid of a built-in computational device; a probe using fiber optics to detect colorimetric changes was designed to permit pH measurements in vivo; a special-purpose colorimeter has been constructed to extend the applicability of enzyme-linked immunosorbent assay (ELISA).

Advances in instrumentation and models for evaluating biologically relevant physical properties have also been made: fiber optic technology was employed to develop a microspectrophotofluorometer for study of changes in local tissue perfusion by using fluorescein as tracer; an electrochemical technique was applied to flow measurements to provide experimental verification for mathematical models of shear stress and velocity profiles in arterial geometries; a solid state pressure transducer was built to correlate experimental results with an analytical model which relates systemic arterial pressure to dynamic intracranial pressure; bone cells were cultures on synthetic deformable membranes so that effects of time-varying strain upon patterns of orientation could be determined; studies were begun on a similar apparatus to study transmembrane mass transport induced in aortic endothelium by applying shear stress.

Analyses of physiological processes have been advanced significantly by a number of related theoretical and experimental studies. Principles of chemical engineering continue to be applied to pharmacokinetics; the distribution in vivo and the fate of hazardous agents in the environment, for example, kepone and several chlorinated biphenyls, have been explored; transport and diffusion of chemotherapeutic agents such as cis-dichlorodiammine-platinum (II) and methotrexate have also been studied; pharmacokinetic criteria have been established for intraperitoneal administration of antineoplastic agents. Improvements have been made in the methodology of hollow fiber cell culture to measure changes in oxygen consumption in response to pharmacological agents. The same technological base has been used to develop a versatile family of tissue/organ life support systems. Mathematical models are being developed to describe passive membrane transport through pores or gap junctions and to provide physical explanations for phenomena such as hindered diffusion. Mechanical devices are being designed to permit studies of visual tracking in human beings and to investigate visual-vestibular interactions.

Projects of clinical relevance, with respect to either diagnosis or treatment, continue to engage a substantial fraction of BEIB's staff. Noteworthy progress has been made in understanding the interaction of polymers used in implants with their physiological environments. Important improvements have been made in the real-time mechanical ultrasound scanner. It has proved to be highly effective in several types of procedures--ocular, cardiac and abdominal. Indeed, preliminary evidence suggests strongly that is is superior to whole-body CAT scanning for rapid assessment of tumor size. Catheters as small as 1 mm in diameter are being developed for insertion into small tortuous vessels with minimal trauma to the vessel wall. Improved vitrectomy apparatus is being developed. A major contribution has been made to the extended use of hyperthermia in the treatment of inoperable neoplasms; careful maintenance of stable elevated whole body temperatures is made possible by a programmable calculator which regulates and monitors control procedures.

Research support functions performed by the technical service sections have also increased. In response, the professional engineering staff assigned to those sections has been augmented to improve service to biomedical investigators. In addition, greater stress has been placed on training of technical staff and direct involvement with professional engineers. Individual initiatives and participation in the technical design phases are encouraged. Contracting has been further expanded to take care of the major part of routine fabrication, systems maintenance and repair. Allocation of a greater proportion of BEIB resources on a temporary basis has increased flexibility and thereby reduced backlogs in the Systems Maintenance Section to two days and in the Instrument Fabrication Section to about four weeks. While it may be possible to expand contracting somewhat, it would not be an effective method of reducing costs if applied to the bulk of novel devices built by IFS. The Scientific Rental Program expanded by about 40% in number of rental contracts and 25% in equipment utilization rate. Efforts are being made to enlarge the inventory of devices most commonly required by NIH investigators.

II. BRANCH PROGRAMS

A. Current Programs: Progress and Accomplishments

1. Engineering and Applied Science

a. Chemical Engineering Section

The Chemical Engineering Section provides a broad range of theoretical, experimental, design and consultative services including physiologic systems and transport phenomena, analytical methodology, biomaterials and specialized instrumentation.

The section has developed significant new methodology in the application of chemical reaction engineering to a variety of pharmacokinetic problems. The approach is widely recognized in the scientific community. At present our expertise in pharmacokinetic modeling is a resource which has become an integral part of the programs and planning of several NIH components. Particular emphasis has been placed on extrapolation of the pharmacokinetics of environmental contaminants from animals to man and continuing support of both laboratory and clinical anticancer drug protocols.

The following pharmacokinetic projects were undertaken this year: (1) A model was developed for the distribution and disposition of kepone in the rat after intravenous or oral administration. An important mechanism of elimination may be diffusion of kepone directly from the blood to the gut lumen. (2) The model developed for several chlorinated biphenyls in the rat is being extended to the dog and the monkey. Success in these species will strengthen confidence in its applicability to human beings. (3) A pharmacokinetic model has been developed for the distribution and disposition of platinum derived from cis-dichlorodiammineplatinum (II) in the beagle dog. Rapid decrease of kidney clearance *in vivo* correlates with a reduction of filterability *in vitro* and is kinetically consistent with the hydrolysis of one chlorine atom from the complex. (4) Successful use of previously invented devices for continuous administration of methotrexate was reported in a number of studies. Understanding of the biochemical and cellular dynamics of bone marrow exposed to methotrexate was significantly extended. Preliminary success has been achieved with a new device for controlled administration of thymidine. (5) Transport of methotrexate in the Lewis lung tumor in mice is facilitated and saturable *in vivo*, consistent with our model used to elucidate methotrexate transport in several normal and neoplastic tissues. (6) A pharmacokinetic rationale has been established for intraperitoneal administration of antineoplastic drugs for treatment of disease confined to that area. Theoretical calculations suggest that steady-state concentrations may be one to three orders of magnitude higher in the peritoneal fluid than in the plasma for a variety of drugs.

Study of transport phenomena is our smallest program at present but merits emphasis because we have obtained fluid mechanical correlates of atherosclerosis and believe that synthetic membrance technology will have a profound constructive influence on biomedical research. Therefore, we are supporting some independent research to develop mathematical models for passive transport through pores and intracellular gap junctions. The studies will strengthen our ability to respond to requirements for instrumentation involving synthetic membranes and may also enhance biological understanding of the phenomena.

Data on wall shear rate distribution in a cast of a canine aorta have been compared with experimental measurements in an idealized version of the flow model and with solutions of the Navier-Stokes equations obtained by finite-element numerical techniques. The pattern of shear in the two side branches of the idealized model mimicked shear patterns observed in the celiac and anterior mesenteric branches of the canine model; however, flow reversal and separation, previously seen at the protruding mesenteric flow divider lip, did not occur. The finding emphasizes the dependence of shear on details of the intricate geometry of the flow. Results of the numerical solution agree with the wall shear magnitude and distribution observed in the canine model and provide an estimate of the velocity profiles.

Regular and singular perturbation techniques and collection techniques have been applied to the hydrodynamic problems in porous membranes, while the transport analysis has involved the Taylor-Aris dispersion treatment and method of moments. Leading terms in the asymptotic expressions for the dispersion analysis transport coefficients have been evaluated for a neutral spherical solute in a slit with plane parallel boundaries, a geometry suggested by electron micrographs of endothelial gap junctions.

Considerable effort was devoted to instrumentation and measurement techniques. This program area provides instrumentation and analytical methodology to a variety of laboratory and clinical studies. Major projects in which we have significant investments include quantification, identification and characterization of trace metals in biological tissues; instrumentation for high density tissue culture; and development of implantable sensors for measurements of tissue pH.

Our facility for analysis of trace metals by flameless atomic absorption is in continual use by our staff and other NIH investigators. We have also developed close collaboration with the National Bureau of Standards to utilize their nuclear reactor facilities and expertise for analysis of trace metals in biological specimens by neutron activation analysis. Fractionation of platinum-containing chemical substances and quantitation of the fractions are providing qualitative insight into the transformations that occur and quantitative information about their kinetics. Studies of the effect of polyamines on the inhibition of enzymes have required analysis of magnesium at low concentrations. A biochemical study of relative calcium- and magnesium-binding affinities to cyclic-AMP precursors by equilibrium dialysis involved quantitation of the inorganic materials. In addition, the iron content of a purified enzyme has been confirmed.

Instrumentation has been developed for monitoring the rate of oxygen consumption in a hollow fiber tissue culture unit. The instrumentation employs a Clark-type amperometric oxygen electrode. It supports studies to improve methodology for high-density tissue culture and investigate the response of cultured cells to pharmacologic agents.

A miniature pH sensor has been designed which will pass through a 22-gauge needle and can be implanted in tissue for physiological studies. The sensor is based upon dye indicators of pH and incorporates fiber optics connected to an electro-optical measuring and readout system.

The NIH has developed competence to meet its requirements in biomaterials over a period of many years. The biomaterials program is used by investigators studying a wide range of problems in laboratory science and clinical medicine. It serves as a vital link between the biological scientist and the industrial and academic components of the materials field. The pioneering application of segmented polyurethane to biomedical prostheses has received further validation through implant studies. Blood contacting surfaces in heart-assist pumps perform well in calves. No lipid absorption is observed; physical strength remains stable; and surfaces develop a biocompatible layer of protein. Coverings of segmented polyurethane on emergency transthoracic pacemaker leads have remained intact, electrically insulating and biocompatible when tested acutely for 15 days.

b. Electrical and Electronic Engineering Section

This section is primarily concerned with making available to the NIH intramural research program the full power of modern electronic technology. Activities include design and construction of new devices, assistance with selection and application of commercially available apparatus, systems analysis, management of research and development contracts and production contracts, planning special programs such as one regarding electrical safety for patients, and consultation and communication with NIH researchers and members of the electronic profession. The scope of work embraces analog and digital circuit design, software development in conjunction with microprocessors. transduction, feedback control systems, video and radio frequency circuitry, laser systems, image processing, telemetry, electrical safety and many other fields.

In the area of diagnostic ultrasound, a second generation real-time mechanical sector scanner with electrically programmable scan was developed and work was done on a solid-state scan converter to produce a standard video signal. These two devices, used in conjunction with additional video components such as monitors and tape records, will provide a system that overcomes the previous limitations of mechanical sector scanners at a cost far below that of nonreal-time systems using other approaches. In addition, the configuration will be ideal for incorporation of Doppler velocity measurement capability and is adaptable to cardiovascular, abdominal and ocular use. Thus, a high level of functional power will be achieved at nominal cost, a factor of rapidly increasing importance.

A second clinical development of major importance was instrumentation for monitoring, data logging, calibration and control of hyperthermia treatment of cancer patients. The project has been carried to the point needed to support pilot studies to verify the potential of the method. Further development to reduce manpower requirements will be made if initial results of clinical trails are positive.

A new area of major emphasis in the patient electrical safety program included computer analysis of the large body of test data accumulated previously. Activity to develop and interpret standards has increased greatly.

Turning to laboratory instrumentation, major progress was made on microprocessor-based instruments. Software research facilities were strengthened and relocated to advantage, while additional staff members received formal training and acquired experience. An oxygen dissociation analyzer built last year was further developed, and two new instruments were completed. One controls the operation of a microcalorimeter and processes the data. The other performs similar functions with a blood gas analysis instrument incorporated within a life support system. Substantial progress was made on other microprocessor systems, including an elaborate system for monitoring animal motor activity and temperature as well as certain physiological parameters. A thermistor temperature-measuring device is being developed that will possess all the desired features of both a.c. and d.c. bridges while eliminating undesirable features, such as the need for manual resistive and capacitive balancing of a.c. bridges and the sensitivity to thermoelectric electromotive forces and amplifier drift of d.c. bridges. In addition, the microprocessor will allow precise control of self-heating, a wide range of operation, precision linearization and several data-handling functions.

An important new instrument was designed and built to perform the recently introduced enzyme-linked immunosorbent assay(ELISA). As a replacement for methods relying on radioactivity, this approach has tremendous potential. Two instruments were built and plans have been provided to commercial manufacturers. More sophisticated instruments are under development to facilitate extension of the techniques to other immunological systems.

Other projects of interest include design of apparatus for use in studies attempting to evaluate the merits of proton radiography, a dual-wavelength blood oximeter with five-microseconds response time for use in laser photolysis experiments, special function generating equipment for a Mossbauer spectrometer, several subsystems of a laser T-jump apparatus, and a special-purpose electronuclear double resonance (ENDOR) system.

Substantial effort was devoted to modification, improvement and extension of programs initiated in previous years. The biggist such effort was expansion of a system for identification and behavioral study of rats. The number of portals at which individual rat identification can be made was increased from 20 to 80.

c. Mechanical Engineering Section

A new device was developed for pulling glass micropipettes. Pipette-forming machines now available must produce stems of excessive length and fragility in order to form tips of sufficiently small diameter. On the new device, electronic controls and photosensing controls which monitor temperature, together with counterbalanced springs, produce tips with a stem taper held to approximately three millimeters.

A new and simplified connector was designed for molecular models. It permits "molecules" to be "bonded" to each other about the bond axis to within a 5° angular error. These joints, or bonds, are easily adjustable for corrective realignment. The new system facilitates the building of molecular models used to visualize protein structure in three dimensions.

A laminar flow proportional amplifier is being developed to provide temperature sensing in microcalorimetry systems. The device is used to determine sources of unwanted pressure drops and fluid heating in microcalorimeters. In addition, such sensing provides finer control of the fluid velocities in the calorimeters. The method used depends upon minute viscosity changes in a capillary tube. Using air as the sensed fluid, temperature measurements in the range of $0.001^{\circ}C$ are achievable. If liquid is used, sensitivity will be increased.

A new group of test tube plugging machines has been developed. They permit the mass handling of sterile tubes used to hold agar slants. Five tube sizes can be handled simultaneously, and one or more tube sizes can be processed independently of the remainder. Sensors, trouble lights and independent controls permit the machine to sense faults, such as tubes picked out of a feed hopper in reversed position, and stop operation until the error is corrected without closing down the entire system.

A special chamber for small animals has been designed. It permits controlled exposure of mice to small quantities of an expensive gas, O_2^{18}. The experiments for which this apparatus has been developed are part of a study of hormone feedback loops involving serotonin. In order to examine the metabolism of serotonin in mice, a sealed life support system is required in which the test atmosphere is precisely formulated and controlled. This requirement is particularly necessary when using the indicated tracer gas.

A drawing and sketching attachment to a microscope is in development. It is particularly designed to facilitate neuroanatomical studies. Linear encoders drive an X-Y recorder as the operator follows and plots from tissue sample slides. Alternatively, a joy-stick controller will be added to make possible continuous, manual curvilinear tracing.

A study concerned with quantitating dysfunctions in patients before and after therapy is being instrumented. The intent is to measure improvements resulting from treatments. A limb plethysmograph provides the sensing device. The limb, generally a forearm, is placed in a water- or air-filled, sealed chamber. Pressure waveforms are then monitored and recorded for

later compariosn. Since a plethysmograph operates by observing the pulsatile waveform brought on by changes in blood flow and pressure, which in turn are controlled by the peripheral nervous sytem constricting the arterioles, it should be possible to elicit much more information from the waveforms than that currently obtained. By examination of the fine structure of the waveforms produced by the peripheral nervous system, examination of the general "tone" or well-being of a patient may be possible.

d. Florence Agreement

BEIB implements NIH commitments related to the "Florence Agreement." Responsibilities include review of applications for duty-free entry of foreign manufactured scientific apparatus acquired by domestic nonprofit institutions, assessment of the suitability of the equipment for intended applications, investigation of availability of domestically produced scientific equivalents, recommendations to the U.S. Department of Commerce for approval, disapproval or resubmission and providing pertinent technical advice to requesting agencies and the Department of Commerce.

Complete statistics for FY 1977 are not yet available, but the total number of applications processed will probably be 400 to 500. The rate of applications decreased markedly during the last quarter of 1976, increased somewhat in the first quarter of 1977 and increased sharply in the second quarter.

BEIB continues to develop standardized test specimens and compounds to use in assessment of new instruments available commercially and relative capabilities of domestic and foreign instruments.

2. Technical Services

During the last five years the number of jobs processed by Technical Services has remained constant; however, the complexity, technical skill and time required for many of these jobs has been gradually increasing. It is anticipated that this increase in complexity will continue for at least the next few years. In order to meet these demands, Technical Services is contracting out a greater number of jobs and is placing a greater emphasis on employee training and development.

a. Instrument Fabrication Section

Contracting of repeat fabrication jobs and some of the less complex fabrication jobs has resulted in reducing the backlog for nonurgent requests from eight to approximately four weeks. It is anticipated that the backlog will continue to be reduced. Urgent projects and all programs related to patient care continue to receive first priority.

b. Systems Maintenance Section

Through the use of contracting, the backlog has been reduced to the lowest possible level consistent with efficient scheduling of employee time. Urgent requests are responded to the same day while the backlog for routine work is about two days.

The Scientific Equipment Rental Program has continued to expand over the year as summarized below:

	July 1, 1976	July 1, 1977	Percent Increase
Number of pool items	590	650	10%
Dollar value	$850,000	$850,000	0%
Number of items on rental (Yearly average)	268	380	42%
Utilization rate (Yearly average)	45.5%	58%	25%

c. Supply Unit

Reviews of the stockroom and special procurement ordering procedures have been completed. Approximately 5% of the stockroom items are out of stock at any given time, and a significant number of items ordered are received after the quoted date.

To reduce the number of items out of stock, a system has been initiated to adjust the frequency and amount of stockroom items ordered to the rate of usage and previous delivery time. Procedures have also been instituted to expedite orders and reduce average delivery time.

3. Selected Technical Advances

An interface unit to allow performance of coulometrically-controlled potentiometric titrations under control of a microprocessor.

A combination ultrasonic system for two-dimensional cardiac imaging and pulsed Doppler velocimetry. The data allow phasic estimation of both left heart and right heart stroke volume. In addition, details of the velocity waveform are available for comparative studies in various disease states.

A pneumatically actuated device designed to deliver controlled strain-rate loading of the spinal cord of the cat.

An analytical model of the free diffusion of potassium in the cat cortex after monopolar electrical stimulation.

A temperature logging and display system for hyperthermia treatment of cancer patients with resolution to 0.01 degree Centigrade and visual and audible alarms.

Development of a mathematical model to describe the distribution and disposition of polychlorinated biphenyl isomers in the rat. The model is designed to be directly applicable to other mammalian species including the human.

A theorectical and experimental study of shear stress distribution in a plasti model of the canine aorta.

Design, construction and testing of an Emergency Transthoracic Pacing Electrode with the advantage of positive fixation, intimate electrical contact, maintenance of low threshold levels and minimal insult to the myocardium.

Design and fabrication of a high-speed (450,000 RPM), rotating optical polarizer used in the measurement of fluorescence activity in isolated neural membranes during electrical stimulation.

Design and fabrication of a single-cell, thermal pH titration apparatus used to study exothermic reactions and pH changes during acid/base titration of protein solutions.

A major new instrument for oxygen dissociation studies of human blood. The experiment is carried out under microprocessor control with program control of some parameters and feedback control of others. Data is logged and displayed for monitoring during the experiments. Subsequently, bound oxygen vs. total oxygen is calculated and plotted, and this information plus rate data is transmitted to a separate digital system for storage.

A visual stimulation system comprising a CCTV monitor and a special-purpose video generator which creates checkerboard patterns of selectable coarseness, with the relative intensities electrically programmable. Evoked potentials will be cross-correlated with the intensity control signal to determine certain neurological parameters.

An improved optical device adapted to an experimental goniopuncture Q-switched laser.

A study of complex equilibria of Mg++ with several nucleotides; development of a method of analysis for Mg++ in the range of 0.5-20 parts per billion.

A microprocessor-based instrument for use with a blood gas analyzer transducer developed with the Laboratory of Technical Development, NHLBI. The instrument controls and acquires data from the transducer, and a thermistor processes the data to obtain pO_2 and pCO_2 and outputs the results to recording and display devices. The instrument also calculates the running averages of the previous five values and displays either this average or the current value. In addition, the instrument receives oxygen saturation voltages from two sites, scales the values and displays them digitally.

A photometer for use in reading ELISA tests. The unit consists of a manually operated positioner for a 96-well microtiter tray and optical system for performing relative absorbance measurements at 420 nm, and a printing digital voltmeter to record results. Measurements can be made much faster than with a spectrophotometer with the added advantage that the specimens are left undisturbed for further study.

A high-precision differential thermistor bridge for use in differential calorimetry. The unit includes built-in oscilloscope and digital voltmeter to facilitate use, as well as provisions for employing the thermistors as heaters for initial equilibration.

A high-speed dual-wavelength transmission oximeter for photolysis studies of oxygen binding by hemoglobin.

A digital readout device coupled to the micrometer dial of a hydraulic microelectrode drive. Electrode position can be determined while doing visual studies in a dark environment and offers a resolution of 1 micron with no error through the range of 1 to 10,000 microns.

4. Training

An effective professional and technical training program helps BEIB maintain a high quality of engineering and technical service support. BEIB employees participated in 72 academic, administrative and technical courses, including 17 formal university courses taken for credit. Whereas 15 employees received specialized training on scientific equipment from various manufacturers, 47 attended administrative, clerical, technical and scientific seminars and short courses and 2 are currently enrolled in Upward Mobility College.

B. Program Plans

BEIB has the primary responsibility to provide engineering support and technical services to the intramural program of the NIH. Specific activities reflect both the needs of NIH and the human and material resources available to the Branch. As these resources are expected to remain severely limited for the immediate future, the Branch must attempt to optimize their use through closer and continuing interaction with NIH scientists in defining and pursuing those areas of development that are likely to be significant.

It must also coordinate and direct constructive relationships with other government agencies, universities and the private sector. Further, the Branch staff must be alert to opportunities for the development of new technology. It requires an environment in which creativity and initiative are both recognized and rewarded.

BEIB plans pertain both to engineering and technical services:

1. Emphasize projects that have been known potential for significantly advancing our ability to (a) observe, describe and analyze biological systems or (b) provide technology to clinical medicine.

2. Encourage initiatives in developing new technology relevant to the mission of the Branch.

3. Develop our staff through in-house training, short courses, advanced study, research and participation in professional and technical societies.

4. Exploit resources of other government agencies and private companies for

contract of routine and production-type work and for required capabilities not available in-house.

5. Use outside staff on short-time or slot-free assignments such as through the Visiting Program, Intergovernmental Personnel Act, Stay-in-School Program, New Careers Program and Guest Worker Program.

C. Publications and Patents

1. Publications

Allen, H.D., Goldberg, S.J., Sahn, D.J., Henry, W.J. and Griffith, J.M.: Medium for External Acoustic Transmission. In White, D. and Barnes, R. (Eds.): Ultrasound in Medicine. New York, Plenum Press, 1976, Volume 2, pp. 107-108.

Bungay, P.M., Dedrick, R.L. and Guarino, A.M. Pharmacokinetic modeling of the dogfish shark (Squalus Acanthias): distribution, urinary, and biliary excretion of phenol red and its glucuronide. J. Pharmacokinet. Biopharm. 4: 377-388, 1976.

Dvorak, J.A., Schuette, W.H. and Whitehouse, W.C.: The application of low light level video techniques to biomedical research. Low Light Level Devices SPIE 78: 155-160, 1976.

Goldstein, S.R., Grantham, F.H., Hill, D.M. and Gullino, P.M.: A fiber optic micro-spectrophotofluorimeter for in vivo animal studies. Proc. 29th Annual Conf. Engr. Med. Biol. 18: 440, 1976.

Griffith, J.M. and Brody, W.R.: Resolution performance of pulsed ultrasound Doppler blood flowmeters. In White, D. and Barnes, R. (Eds.): Ultrasound in Medicine. New York, Plenum Press, 1976, Volume 2, pp. 277-279.

_____, Vita, A.J. and Henry, W.L.: A moving-trace design for video systems. IEEE Trans. Biomed. Eng., November, 482-484, 1976.

Harder, H.C., Smith, R.G. and LeRoy, A.F.: Template primer inactivation by cis- and trans-dichlorodiammine platinum for human DNA polymerase α, β, and rausher murine leukemia virus reverse transcriptase as a mechanism of cytotoxicity. Cancer Res. 36: 3821-3829, 1976.

Henry, W.L., Maron, B.J., Griffith, J.M. and Epstein, S.E.: Identification of double outlet right ventricle by two-dimensional echocardiography. Clin. Res. XXIV: 222, 1976.

Jernigan, M.E. and Eden, M.: Model for a three-dimensional optical illustion. Percept. Psychophys. J. 20: 438-444, 1976.

Kagan, R.L., Schuette, W.H., Zierdt, C.H. and MacLowry, J.D.: Rapid automated diagnosis of bacteremia by impedance detection. J. Clin. Microbiol. 5: 51-57, 1977.

Kollarits, C.R., Goldman, H., Murphy, S. and Kollarits, F.J.: Use of ^{14}C-antipyrine for estimation of rhesus monkey eye bloodflow. Invest. Ophthalmol. 15: 740, 1976.

Leighton, S.B.: Cerebrospinal fluid, superior sagittal sinus and central venous pressure as a function of the angular position of the body. Proc. 29th Annual Conf. Engr. Med. Biol. 18: 377, 1976.

Lewis, D.V. and Schuette, W.H.: NADH Fluorescence, $[K+]_o$ and oxygen comsumption in cat cerebral cortex during direct cortical stimulation. Brain Res. 110: 523-535, 1976.

Litterst, C.L., Gram, T.E., Dedrick, R.L., LeRoy, A.F. and Guarino, A.M.: Distribution and disposition of platinum following intravenous administration of cis-diamminedichloroplatinum (II) (NSC 119875) to dogs. Cancer Res. 36: 2340-2344, 1976.

_____, _____, Guarino, A.M., Mimnaugh, E.G., LeRoy, A.F., and Dedrick, R.L.: Disposition of platinum following IV administration of diamminedichloroplatinum to dogs. The Pharmacologist 18: 195, 1976.

Lutz, R.J., Galbraith, W.M., Dedrick, R.L., Shrager, R. and Mellett, L.B.: A model for the kinetics of distribution of actinomycin-D in the beagle dog. J. Pharmacol. Exp. Ther. 200: 469-478, 1977.

Mutsuga, N., Schuette, W. and Lewis, D.V.: The contribution of local blood flow to the rapid clearance of potassium from the cortical extracellular space. Brain Res. 116: 431-436, 1976.

Peterson, J.I.: Combustion instruments for preparing samples for liquid scintillation counting. J. Chem. Ed. 54: A89-A108, 1977.

Pinedo, H.M., Zaharko, D.S., and Dedrick, R.L.: Device for constant Sc infusion of methotrexate: Plasma results in mice. Cancer Treat. Rep. 60: 889-893, 1976.

Sahn, D.J., Henry, W.L., Allen, H.D., Griffith, J.M. and Goldberg, S.J.: The comparative utilities of real time cross-sectional echocardiographic imaging systems in complex congenital heart disease. In White, D. and Barnes, R. (Eds.): Ultrasound in Medicine. New York, Plenum Press, 1976, Volume 2, pp. 75-76.

Schmidt, E.M., Mutsuga, N., McIntosh, J.S., Kanda, K. and Goldstein, S.R.: Intracellular recording from pulsating cerebral cortex. Electroencephalogr. Clin. Neurophysiol. 42: 581-583, 1977.

Schuette, W., Norris, G., and Doppman, J.: Real time two-dimensional mechanical ultrasonic sector scanner with electronic control of sector width. Society of Photo-Optical Instrumentation Engineers 96: 345-348, 1976.

Schuette, W.H., O'Connor, M., Lewis, D.V., and Van Buren, J.M.: The design and operation of a dual-beam long-focal length fluorometer for monitoring the oxidative metabolism in vivo. Med. Biol. Eng., March, 235-238, 1976.

_____, Vern, B. and Whitehouse W.C.: A television fluorometer for evaluating oxidative metabolism of exposed myocardium in vivo. In Proceedings of the Association for Advancement of Medical Instrumentation 12th Annual Meeting, San Francisco, March 1977, p. 50.

_____, _____, and _____: A low-light television system for the in vivo measurement of oxidative metabolism as indicated by NADH fluorescence. App. Optics in Med. and Biol. 89: 47050, 1977.

Vern, B.A., Schuette, W.H., Whitehouse, W.C. and Mutsuga, N.: Cortical oxygen consumption and NADH fluorescence during metrazol seizures in normotensive and hypotensive cats. Exp. Neurol. 52: 83-99, 1976.

Zaharko, D.S., Dedrick, R.L., Young, D.M., and Peale, A.L.: Tolerance of long-term methotrexate infusions by mice. Biochem. Pharmacol. 25: 1317-1321, 1976.

2. Patents

Tipton, H.W. and Peterson, J.I.: "Method and Apparatus for Cutting Cyclinders of Gelatinous Materials into Discs of Precise Thickness." U.S. Patent No. 3,954,033 (May 1976).

Tipton, H.W.: "Radiation Safety Shield Syringe." U.S. Patent No. 3,973,554 (August 1976).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10001-09 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Pharmacokinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L. Dedrick	Chief	ChES BEIB DRS
OTHER:	D.S. Zaharko	Pharmacologist	LCHPH NCI
	R.A. Bender	Oncologist	MB NCI
	A.M. Guarino	Chief	LT NCI
	R.J. Lutz	Chemical Engineer	BEIB DRS
	A.F. LeRoy	Chemical Engineer	BEIB DRS
	K.B. Bischoff	Prof., Biomed. & Chem. Engr.	Univ. of Delaware
	M.W. Anderson	Mathematician	EB NIEHS
	T.E. Eling	Pharmacologist	PB NIEHS
	P.M. Bungay	Chemical Engineer	BEIB DRS
	W.M. Galbraith	Pharmacologist	FDA
	H.B. Mattews	Pharmacologist	PB NIEHS
	W.A. Bleyer	Oncologist	Univ. of Wash.
	C.E. Myers	Oncologist	CPB NCI
	I.J. Torres	Guest Worker	LT NCI

COOPERATING UNITS (if any)

LCHPH-NCI; LT-NCI; PB-NIEHS; AK-CU Program NIAMDD; University of Washington; M-NCI; EB-NIEHS; FDA; University of Delaware; CPB-NCI.

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Pharmacokinetic models are developed for the distribution and diposition of drugs, environmental contaminants and endogenous metabolites in animals and man. They provide a plausible set of equations that can be used to extrapolate from animals to man and thereby to improve chemotherapy and hemodialysis.

Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants and endogenous metabolites in animals and man to:

(1) Account for species differences in drug distribution.

(2) Provide rational bases for extrapolation of toxicity from animals to man.

(3) In conjunction with pharmacodynamics, provide a basis for optimization of cancer chemotherapy and long-term hemodialysis.

(4) Enable rational transfer of *in vitro* thermodynamic and kinetic data to *in vivo* cases.

(5) Predict effective dose schedules of anticancer drugs in individual patients with particular emphasis on intraperitoneal drug administration.

Methods Employed: Mathematical models are developed from physicochemical, physiological and anatomical information and the principles of chemical reaction engineering. Resulting sets of differential equations are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

Major Findings: (1) A pharmacokinetic model was developed for the distribution and disposition of Kepone in the rat. Compartments include blood, liver, fat, muscle and skin. In addition, a four-compartment gut lumen permits simulation of a physiological residence-time distribution and quantitation of transport rates between gut contents and blood. Model parameters determined at one hour and seven days after single intravenous doses of 1 mg/kg and seven days after oral administration of the same dose were used to predict pesticide concentrations at forty-five days following four daily oral doses of 10 mg/kg. Transport from the blood to the gut contents may be an important mechanism of elimination.

(2) The pharmacokinetic model developed for the distribution and disposition of several chlorinated biphenyls in the rat has been thoroughly documented. A contract has been awarded to obtain data for extension of the model to the dog and to the monkey. Many of the model parameters are physiologic or anatomic and are not dependent upon a particular environmental contaminant. Others, such as thermodynamic distribution coefficients, may be very similar among mammalian species. Intrinsic metabolic rates are embedded within the model so that they have a natural and fundamental definition not obscured by distribution effects.

(3) A pharmacokinetic model has been developed for the distribution and disposition of platinum derived from cis-dichlorodiammine platinum (II) in the beagle dog. Renal clearance of platinum decreases rapidly. This decrease correlates with a change of filterability of platinum in vitro which is kinetically consistent with the hydrolysis of one chlorine atom from the square-planar complex. This hydrolysis step is probably essential to activation of the drug and, together with the concomitant change in binding, explains the profound decrease in platinum elimination kinetics.

(4) A number of studies were reported which employed previously invented implantable devices for continuous controlled administration of methotrexate to experimental animals. These studies included achievement of plateau concentration in mice from 10^{-8} to 10^{-5} M. Understanding of the biochemical and cellular dynamics of bone marrow exposed to methotrexate was greatly extended. Preliminary success has been achieved with a new implantable diffusion cell for continuous administration of thymidine.

(5) Transport of methotrexate in the Lewis lung tumor in mice has been examined in vivo over a dose range of 0.003 to 300 mg/kg Transport is facilitated and saturable, consistent with the model used to elucidate methotrexate transport in spontaneous canine lymphosarcoma and bone marrow, spleen and gastrointestinal tract of the rat in prior studies.

(6) A pharmacokinetic rationale has been established for intraperitoneal administration of antineoplastic drugs for treatment of disease confined to this area. Theoretical calculations suggest that steady-state drug concentrations in the peritoneal cavity may be one to three orders of magnitude greater than plasma concentrations for a variety of hydrophilic anticancer drugs. This is a potentially exploitable difference analogous to that obtained by intrathecal drug administration in treatment of meningeal leukemia.

Significance: Drugs and other chemicals are tested for effects in animals the extrapolation to man is a subject of serious concern. Both risks are both the risk associated with environmental contaminants and optimal of therapy.

Proposed Course: Continued pharmacokinetic modeling with consideration of pharmacodynamic and cytokinetic events. Continued clinical emphasis through support of high-dose and intraperitoneal protocols and other attempts to overcome drug resistance. Increased emphasis on research designed to investigate distribution of environmental contaminants.

Publications:

Zaharko, D.S., Dedrick, R.L., Young, D.M. and Peale, A.L.: Tolerance of Long Term Methotrexate Infusions by Mice. Biochem. Pharmacol. 25. 1317-1321, 1976.

Zaharko, D.S. and Dedrick, R.L.: Antifolates: In Vivo Kinetic Considerations. Cancer Treat. Rep. 61: 513-518, 1977.

Bleyer, W.A. and Dedrick, R.L.: The Clinical Pharmacology of Intrathecal Methotrexate (NSC-740) I. Pharmacokinetics in Nontoxic Patients after Lumbar Injection. Cancer Treat. Rep. 61: 703-708, 1977.

Litterst, C.L., Gram, T.E., Dedrick, R.L., LeRoy, A.F. and Guarino, A.M.: Distribution and Disposition of Platinum Following Intravenous Administration of cis-Diamminedichloroplatinum-II (NSC-119875) to Dogs. Cancer Res. 36: 2340-2344, 1976.

Bungay, P.M., Dedrick, R.L. and Guarino, A.M.: Pharmacokinetic Modeling of the Dogfish Shark (Squalus acanthias): Distribution, Urinary, and Biliary Excretion of Phenol Red and its Glucuronide. J. Pharmacokinet, Biopharm. 4: 377-388, 1976.

Pinedo, H.M., Zaharko, D.S. and Dedrick, R.L.: Device for Constant Sc Infusion of Methotrexate: Plasma Results in Mice. Cancer Treat. Rep. 60: 889-893, 1976.

Lutz, R.J., Galbraith, W.M., Dedrick, R.L., Shrager, R. and Mellett, L.B.: A Model for the Kinetics of Distribution of Actinomycin-D in the Beagle Dog. J. Pharmacol. Exp. Ther. 200: 469-478, 1977.

Lutz, R.J., Dedrick, R.L., Matthews, H.B., Eling, T.E. and Anderson, M.W.: A Preliminary Pharmacokinetic Model for Several Chlorinated Biphenyls in the Rat. Drug. Metab. Dispos. 5: 386-396, 1977.

Stoller, R.G., Jacobs, S.A., Drake, J.C., Lutz, R.J. and Chabner, B.A.: Pharmacokinetics of High-Dose Methotrexate. Cancer Chemotherap. Rep. 6: 19-24, 1975.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10002-12 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Implant Device Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.W. Boretos	Physical Scientist	BEIB DRS
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	D.C. Syracuse	Clinical Associate	SU NHLBI
	W.S. Pierce	Assoc. Professor	Penn State University
	W. Derkac	Clinical Associate	SU NHLBI
	N. Iriguchi	Guest Worker	Asahi Chemical Co.

COOPERATING UNITS (if any)

SU-NHLBI; Pennsylvania State University, Asahi Chemical Co.

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 21104

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.7	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to elucidate the interaction of polymers used for specific implants with the physiological environment and to explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts. After removal from the host organism, implants will be examined for lipid absorption, protein deposition, changes in surface-free energy, and alteration of physical properties. Prostheses such as artificial hearts, heart valves, and catheters will be employed. Observations should include SEM, infrared spectroscopy, contact angle measurements, tensile property measurements, and energy dispersive x-ray analysis.

PHS-6040
(Rev. 10-76)

Objectives: Elucidate the interaction of polymers used for specific implants with the physiological environment; explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts.

Methods Employed: Basic polymer composition is carefully controlled, and modification of cross-linking systems is employed. Rheological properties are studied as a function of cross-linking. After removal, implants are examined for lipid absorption, protein deposition, changes in surface-free energy, and alteration of physical properties. Observations include, SEM, infrared spectroscopy, contact angle measurements, energy dispersive x-ray analysis and atomic absorption spectroscopy. Flow characteristics and pressure gradients across heart valve implants are studied *in vitro* in a test apparatus.

Major Findings: Continued experience with heart-assist devices with segmented polyurethane blood contacting surfaces substantiate its outstanding performance in calves. No lipid absortion is observed; physical strength remains stable; surfaces develop a biocompatible layer of protein.

Coverings of segmented polyurethane on emergency transthoracic pacemaker leads have remained intact, electrically insulating and biocompatible when tested acutely for 15 days.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart-assist devices, vascular implants, and subcutaneous uses.

Proposed Course: (1) Extend experimental studies to further characterize the surface and bulk properties of polyether urethanes and more specifically determine its interactions with blood and subcutaneous tissue; and (2) study new designs of tricuspid heart valves for short- and long-term use.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10003-05 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Trace Element Analysis in Biological Materials

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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	T.E. Gram	Toxicologist	LT NCI
	I.J. Torres	Staff Fellow	LT NCI
	C.M. Young	Veterinarian	LT NCI
	C.B. Klee	Biochemist	LB NCI
	R.D. Hoeldtke	Biochemist	LCN NIMH
	J.M. Ward	Veterinarian	LT NCI
	W. H. Glinsmann	Biochemist	LBS NICHHD
	C. Nakai	Biochemist	LBS NICHHD
	D.A. Becker	Chemist	NBS
	H. Rook	Chemist	NBS

COOPERATING UNITS (if any)

LT-NCI; LB-NCI; LNC-NIMH; LBS-NICHHD, National Bureau of Standards

LAB/BRANCH
Biomeidical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.6	0.4

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Flameless atomic absorption spectrophotometry and neutron activation analysis have been used for quantitation of Pt, Mg, Ca, Fe and some other elements in biological tissues and fluids. The analyses are important in biochemical, pharmacokinetic and binding studies. Very sensitive analytical techniques are necessary because, in most instances, the elements are present in trace concentrations and, in many cases, the sample size is very small as well. Separation techniques including ion-exchange chromatography, solvent extraction and electrophoresis have been used for purification of samples and fractionation and concentration of chemicals prior to analysis and as a means of eliminating substances interfering with trace-level assays.

PHS-6040
(Rev. 10-76)

Objectives: The objective of this work is to improve analytical and identification techniques for metals in biological materials. Detection limits on the order of picograms to nanograms in milligram samples and simplified sample preparation have been sought. Quantitation of platinum, calcium, magnesium and copper has been emphasized; other elements of biological significance are worked with as interst develops.

Methods Employed: Elemental analysis is being performed principally by flameless atomic absorption spectrophotometry. Control of temperatures generated in a graphite furnace as a function of time permits analysis even when considerable molecular and broad-band absorption occurs during combustion. Neutron activation analysis is being used to perform referee analyses.

Ion exchange chromatography and electrophoresis have been used to fractionate samples, with subsequent quantitation of metals in the fractions. With these techniques, improved resolution and analytical sensitivity are expected to permit findings of biological significance.

Major Findings: Fractionation of platinum-containing chemical species and quantitation of these fractions are being performed to help us understand the transformations that occur and their kinetics. The findings may have important implications for the success of cancer chemotherapy utilizing some metal complexes. Biochemical study of relative calcium- and magnesium-binding affinities in cyclic-AMP precursors were made using equilibrium dialysis experiments; quantitation of Ca and Mg was accomplishe by flameless AAS. Studies on the effect of naturally occurring polyamines on the inhibition of enzymes have required accurate analysis of Mg(II) at low temperatures.

Significance: Quantitation, identification and characterization of metals at trace levels in biological tissue samples, often very small, are important in biochemical research and environmental toxicoloty. Quantitati of a specific element in tissues and body fluids can help in understanding drug action and other biochemical processes. Methods being developed off quantitation of stable elements and obviate the need for radiolabeled substances in some instances.

Proposed Course: Extend applicability of direct combustion technique to include more tissue types. Try to minimize or eliminate pretreatment required. Complete analyses for pharmacokinetic modeling of platinum compound, DDP. Perform necessary analyses for elements using neutron activation to confirm flameless atomic absorption spectrophotometry results Expand use of chromatography to purify samples and fractionate and concentrate chemical species under study.

Publications:

LeRoy, A.F., Wehling, M.L., Sponseller, H.L., Friauf, W.S., Solomon, R.E. and Dedrick, R.L.: Analysis of Platinum in Biological Materials by Flameless Atomic Absorption Spectrophotometry. Biochem. Med. (In press).

Litterst, C.L., Gram, T.E., Dedrick, R.L., LeRoy, A.F. and Guarino, A.M.: Distribution and Disposition of Platinum Following Intravenous Administration of cis-Diamminedichloroplatinum (II) (NSC 119875) to Dogs. Cancer Res. 36: 2340-2344, 1976.

Ward, J.M., Grabin, M.E., LeRoy, A.F. and Young, D.M.: Modification of the Renal Toxicity of cis-Dichlorodiammineplatinum (II) with Furosemide in Male F344 Rats. Cancer Treat. Rep. 61: 375-379, 1977.

Harder, H.C., Smith, R.G. and LeRoy, A.F.: Template Primer Inactivation by cis- and trans-Dichlorodiammine Platinum for Human DNA Polymerase α, β, and Rauscher Murine Leukemia Virus Reverse Transcriptase, as a Mechanism of Cytotoxicity. Cancer Res. 36: 3821-3829, 1976.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10004-06 BEI

PERIOD COVERED

July 1, 1976 to September 30, 1976

TITLE OF PROJECT (80 characters or less)

The Role of Fluid Dynamics and Mass Transfer in Development of Atherosclerosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Lutz	Chemical Engineer	BEIB DRS
OTHER:	J.N. Cannon	Assoc. Prof. of Chem. Engr.	Howard University
	R.L. Dedrick	Chief	ChES BEIB DRS
	D.L. Fry	Chief	H IR OD
	K.B. Bischoff	Prof., Biomed. & Chem. Engr.	Univ. of Delaware

COOPERATING UNITS (if any)

Howard University, University of Delaware, OD-IR-NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.5	.3	.2

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The appearance of atherosclerotic lesions at specific locations in the arterial tree has led many investigators to study the relevance of hemodynamic factors in atherogenesis. The purpose of this study is to elucidate the role of fluid dynamics and mass transfer in the onset and development of atherosclerotic plaques. Specifically, the wall shear stress was measured in a plastic model of a canine artery and in an idealized version of this model using an electrochemical technique to determine velocity gradients at the fluid-wall interface. Regions of high shear and of disturbed flow patterns in the model have been shown to correlate with regions of high incidence of lesions in animals on an atherogenic diet. These regions were near branches and flow dividers. The electrochemical technique also allows measurement of wall mass transfer coefficients during pulsatile flow conditions in the model. The mechanism by which various flow patterns mediate increased lipid uptake by the arterial wall must still be determined.

Objectives: Measure shear stress on the inner wall of plastic models of canine arteries during steady flow and correlate data with localization of atherosclerosis as found in experimental animals. Construct mathematical model of arterial geometery in two dimensions and solve the fluid dynamics equations numberically for prediction of wall shear and velocity profiles. Measure wall shear rate in a more idealized version of a branching flow network for comparison to the complicated geometry of a real artery. Measure the effects of shear on the transport rate of macromolecules through simulated aeterial cell membrance surfaces. Measure the average wall mass transfer coefficients of several size molecules during conditions of pulsatile flow in the model artery.

Methods Employed: An electrochemical technique is used, based on an oxidation-reduction reaction at electrodes implanted at a fluid-solid interface in the artery models which determines mass transfer rates of redox ions. Velocity gradients at the wall (shear rate) are calculated from mass transfer rates with suitabl boundary layer equations.

Solutions of the Navier-Stokes equations are found by using finite element numerical techniques where the boundaries of the numerical flow channel duplicate in two dimensions the shape of the experimental canine model. Predictions are made of the wall shear stress and the velocity profiles. The electrochemical technique was also used to measure the shear pattern in an idealized version of the canine model. It consisted of a main flow channel with two adjacent side branches. This design simulated flow in the thoracic aorta, then out the celiac and anterior mesenteric branches.

Results obtained by solving Navier-Stokes equations by finite element numerical techniques agree both qualitatively and quantitatively with the shear patterns and shear magnitudes measured in the canine flow model, which were reported last year. In addition, the numerical techniques provide an estimate of the velocity flow profiles, which are shown to be skewed in the direction of the celiac and mesenteric branches.

Experimental measurements with the idealized version of the canine model indicated a pattern of shear in each of the two adjacent side branches that mimicked, respectively, those observed in the celiac and anterior mesenteric branches of the initial canine model. The shear pattern is probably a result of having two branches adjacent to one another. The idealized model did not show a pattern of flow reversal or separation near the lip of the second flow divider, as occurred at the mesenteric flow divider lip of the other canine models. The flow separation phenomenon was probably absent from the idealized model because the second flow divider lip did not protrude into the main flow channel, as did the mesenteric lip of the earlier model.

Sifnificance: Elucidation of the role of hemodynamics and mass transfer in the onset and development of atherosclerotic plaques is fundamental to the study of vascular disease.

Proposed Course: To measure the average wall mass transfer coefficient of various molecular weight compounds in the canine model under conditions of pulsatile flow. The mass transfer coefficient will be measured for several frequencies of sinusoidal input flow waves and finally for a waveform representing cardiac output. The mass transfer results from the later flow wave will be Fourier decomposed to compare its frequency response.

Correlations will be sought for the mass transfer coefficients as a function of Reynolds number and Schmidt number.

Attempts will be made to devise a mechanical model of the phospholipid cells and determine the effect of shear on transport of macromolecules across whose artificial membranes.

Publications:

Lutz, R.J., Cannon, J.N., Bischoff, K.B., Dedrick, R.L., Stiles, R.K. and Fry, D.L.: Wall Shear Stress Distribution in a Model Canine Artery During Steady Flow. Circ. Res. (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10018-02 BEI

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Particulate Hydrodynamics in Porous Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: P.M. Bungay Chemical Engineer BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical models are being developed to describe passive membrane transport through pores or intracellular gap junctions. The Taylor-Aris dispersion analysis is extended to treat combined Brownian motion and convection in a single pore. The solute particle dimension is assumed to be large compared to that of the solvent molecules and also appreciable in size compared to the lateral pore dimension. The latter condition implies strong "hindered diffusion" and related solute-membrane interaction effects. A key aspect of the analysis is a generalized Einstein relation for predicting axial and radial components of the diffusivity tensor from hydrodynamics solutions for resistance coefficients. Perturbation techniques are used to obtain asymptotic solutions to the hydrodynamic equations, and the method of moments is employed to analyze the solute continuity equation.

PHS-6040
(Rev. 10-76)

Objectives: The objective of this project is to provide the basis for a rigorous, predictive continuum theory for passive transport phenomena in porous membranes which encompass such observations as "hindered diffusion."

Methods Employed: The essence of the approach is an extension of the Einstein continuum analysis for the Brownian motion of spherical molecules in dilute solutions. Einstein derived his predictive relation for the diffusion coefficient from the theoretical expression for the hydrodynamic resistance to translation of a rigid sphere through a homogeneous viscous fluid of infinite extent. The continuum analysis for porous membranes begins with a single solute molecule in a single pore and assumes that the form of Einstein's relationship between the diffusion and resistance coefficients remains valid. However, the presence of the rigid pore wall, in general, increases the hydrodynamic resistance to the translation and rotation of the solute relative to the fluid. The diffusivity is thereby decreased in magnitude until, in the limit, as the solute dimension becomes equal to the lateral pore dimension, the diffusion coefficient falls to zero. When there is, in addition to diffusion, net movement of the fluid through the pore, the hydrodynamic interaction similarly affects the solute flux relative to the solvent flux. The project is concerned with deriving the requisite expressions for the resistance coefficients from hydrodynamic theory as well as developing analyses for diffusive and convective porous membrane transport.

The primary theoretical tools used in the hydrodynamic problems are regular and singular perturbation techniques (typically using the ratio of solute to pore dimensions as the asymptotic expansion parameter) and collocation techniques of the type developed by Weinbaum and Pfeffer.

The transport analysis has been approached using the Taylor-Aris type dispersion treatment and the method of moments for driving expressions for the pertinent coefficients without directly solving the complete solute continuity equation (convective-diffusion equation).

Major Findings: Leasing terms in the asymptotic expressions for the dispersion analysis transport coefficients have been evaluated for the case of a neutral spherical solute in a long slit with plane parallel boundaries. Electron micrograph evidence suggests that slitlike geometry is typical of the junctions between endothelial cells.

Proposed Course: In addition to the models presently under study, it would be desirable to examine a situation in which the solute is a nonspherical body in order to determine how to handle particle orientation and rotational Brownian motion effects. An ellipsoidal solute would theoretically be the preferred choice. A more desirable course is to incorporate into the present models nonhydrodynamical solute-membrane interactions such as electrostatic or London-Van der Waals attractive/repulsive forces.

Significance: Channels (pores, slitlike gap junctions) represent one type of transmembrane transport in physiological systems. The conceptual framework of pore theory is helpful in biology as well as in engineering and the physical sciences.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10019-02 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Instrumentation for Flow-Through Hollow Fiber Cell Culture Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
OTHER:	R.A. Knazek	Senior Investigator	LPP NCI

COOPERATING UNITS (if any)

LPP-NCI

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Biomedical Engineering and Instrumentation

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DRS, NIH, Bethesda, Maryland 20014

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0.2	0.2	

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

As part of studies aimed at improving the methodology for hollow fiber cell culture and investigating the response of cultured cells to pharmacologic agents, instrumentation systems are being developed for measuring relevant culture parameters. Instrumentation has been developed for monitoring the rate of oxygen consumption using a Clark-type amperometric oxygen electrode. Development of an electrode for monitoring the extracellular oxygen partial pressure is continuing. Subsequent parameters to be investigated are pH and carbon dioxide partial pressure.

PHS-6040
(Rev. 10-76)

Objectives: The short-range objective is to develop sensor and instrumentation packages for monitoring cell metabolism and growth parameters of cells culturing in hollow fiber units. The long-range objectives are to (1) elucidate factors which are beneficial to maintaining and promotion growth, and (2) determine the response of cells to pharmacologic agents.

Methods Employed: In the hollow fiber cell culture units employed in this study, the hollow fibers serve as semipermeable membrane barriers between the cultures outside the fibers and nutrient solution perfused through the fiber lumen. The fibers (typically 200 μm ID and 250 μm OD) permit exchange of oxygen, carbon dioxide, nutrients, products of metabolism and other chemical substances ranging in size up to that of proteins like albumin. The fibers are packed roughly parallel and closely spaced such that diffusional distances typically do not exceed 100 μm. The fiber lumens are continuous with an external closed loop containing a nutrient solution and a pump to maintain recirculation of the solution through the pores. In some units two dupicate loops (hollow fiber bundle/reservoir/pump) are used; however, the two fiber bundles are braided together inside a single culture unit. The more complex systems are designed for studying convective as well as diffusive transport in the extracapillary space.

The effort thus far has been to develop the capability to measure (1) the rate of oxygen consumed by the cells in the unit, and (2) the extracellular oxygen tension in the culture. Under steady conditions, the amount of oxygen given up by the nutrient solution in passing through the fibers is a measure of the rate of consumption by the cells. The connecting tubing leading to the unit is of sufficient length so that the nutrient solution at the inlet to the culture unit is essentially saturated with respect to the ambient carbon dioxide-enriched atmosphere. Measuring the difference in the partial pressure of the nutrient solution between the inlet and outlet of the culture unit permits calculation of the rate of delivery of oxygen to the cells using the medium flow rate and oxygen solubility. For this purpose an instrumentation package has been assembled incorporating a Clark-type amperometric oxygen electrode from a commercial blood gas analyzer.

An electrode scheme has been under development for measuring the extracellular oxygen tension. The plan is to provide access for a fine wire electrode to the interior of a single nonporous, gas-permeable fiber in the bundle. The fiber will extend beyond both ends of the bundle and through the walls of the distribution caps covering the ends of the shell. Thus, the fiber will be bathed externally by the nutrient solution inside the caps, but will be exposed to the cell culture inside the shell. The fiber interior will be otherwise isolated and can be filled with a buffer solution appropriate to an electrode pair, such as platinum and silver/silver chloride.

The oxygen-sensitive cathode will be free to move axially inside the fiber so that it can be positioned to sense the nutrient inlet, extracellular and nutrient outlet oxygen levels. Operated in an amperometric mode, the system will function like a miniature Clark-type electrode.

Proposed Course: After satisfactory development of the oxygen monitoring systems, techniques will be examined for measuring other important cell culture parameters. Among the parameters likely to be looked at next are the pH and carbon dioxide partial pressure in the extracellular fluid.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10022-01 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Fiber Optic pH Probe

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.I. Peterson	Chemist	BEIB DRS
OTHER:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
	R.M. Winslow	Senior Investigator	H IR MH

COOPERATING UNITS (if any)

H-IR-MH

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SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A miniature pH sensor has been designed which will pass through a 22-gauge needle and can be implanted in tissue for physiological studies during exercise. The sensor is based upon dye indicators of pH and fiber optics, and is connected to an electro-optic measuring and readout system.

Objectives: Develop a pH sensor for tissue implantation to be used in studies of oxygen transport during exercise.

Methods Employed: A fiber optic measurement of dye indicator response to pH.

Significance: In studies of abnormality in transport of oxygen to tissue by blood during exercise, measurement of oxygen pressure in the tissue can be used to determine the oxygen content of the blood supply via the blood oxygen saturation curve (concentration vs. pressure). Alternatively, measurements of the blood oxygen concentration can be used to determine oxygen pressure by this curve. Since the relation between oxygen pressure and concentration is changed by changes in pH which occur during exercise (shift in the curve with pH, the Bohr effect), it is necessary to incorporate a pH measurement with the oxygen measurement in making use of the curve.

Major Findings and Proposed Course: An optical pH sensor has been developed and tested in vitro. Development of a readout system is underway, and when finished, will allow in vivo testing.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10011-03 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Electrical Safety Program for Clinical Center Patients and Patient Care Areas

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Corsey	Electronic Engineer	BEIB DRS
OTHER:	W.S. Friauf	Chief	EEES BEIB DRS
	C. Strong	Environ. Serv. Officer	CC
	T. Johnson	Administrative Officer	CC
	J.M. Bucolo	Electronic Technician	BEIB DRS

COOPERATING UNITS (if any)
ADM-CC, SMS-BEIB

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	1.0

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An electrical safety program has been established to perform the following functions for the Clinical Center: establish electrical safety standards; test clinical electrical equipment; carry out the directives of the Clinical Center Safety Committee; train nurses and other staff regarding the fundamentals of electricity, electrical shock and grounding; investigate electrical burns and shocks; survey patient environment; provide counsel to medical and nursing staff on purchase of new equipment; participate in the formulation of national safety standards; design test equipment; and modify existing clinical equipment to meet current safety standards.

Objectives: Establish and maintain a patient environment free of shock and burn hazard, assure that clinical equipment does not present an electrical hazard to the patient, assure that clinical equipment and the patient environment are in compliance with the Joint Commission on Hospital Accreditation requirements, carry out the directives of the Clinical Center Safety Committee, provide input to national standards.

Methods Employed: Three-hour annual training seminars are provided for nurses, and thirty minute sessions are provided for other staff members as requested. Input to national standards is provided by participation in the National Fire Protection Association, publisher of the National Electrical Code, and the Association for the Advancement of Medical Instrumentation, publisher of various clinical equipment codes.

Major Findings: The program has uncovered instances of ungrounded equipment, high leakage current, misinformed personnel, poorly designed electronic circuits, unreliable electrical receptacles and unreasonable national standards.

Significance: In critical care areas, such as operating rooms and intensive care units, patients are no longer exposed to equipment or an environment that could be hazardous. In all patient areas, the likelihood of shock or burns has been reduced. We are recommending standards that reflect the user's viewpoint to national organizations.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10007-03 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Investigation of Oxidation Metabolism and Potassium Kinetics in the Cat Brain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Electronics Engineer	BEIB DRS
OTHER:	B.A. Vern	Clinical Associate	CNB NINCDS
	W.C. Whitehouse	Electronics Technician	ADM CC
	N. Mutsuga	Visiting Fellow	CNB NINCDS

COOPERATING UNITS (if any)

CNB-NINCDS; AB-CC

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Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

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3.0	2.0	1.0

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Oxidative metabolism, as indicated by the fluorescence of NADH and oxygen consumption, is being assessed to investigate potassium ion kinetics in the cat brain. Research is being conducted to determine if the potassium clearance process after activation of the cortex is active or passive. Investigations are also being conducted to determine the applicability of the NADH fluorescence technique to exposed myocardium.

PHS-6040
(Rev. 10-76)

Methods Employed: The NADH fluorescence at 470 nM is excited by illumination with ultraviolet light at 360 nM obtained from a high pressure Hg arc lamp. To compensate for blood volume changes within the field of interest, we developed and used a television fluorometer employing fluorescein dye as a reference. The technique, initially used for study of cat brain, is now being applied successfully to exposed myocardium.

A potassium-sensitive microelectrode system was employed for measuring both extracellular and intravenous potassium ion levels.

Direct cortical oxygen consumption measurements were made by cannulation of the sagittal sinus and monitoring the flow rate and hemoglobin saturation of the blood flowing out of the sinus. The calculated ozygen consumption is proportional to the arterial-venous O_2 concentration difference multiplied by the flow rate.

For the Q_{10} experiments the exposed cat hippocampus temperature was neither elevated or lowered by use of a controlled temperature stream of artificial spinal fluid which flowed over the surface of the hippocampus. Surface temperature was monitored by a small thermistor probe.

Major Findings: The NADH dynamics observed in the myocardium is similar to that observed in the cortex.

Blood volume in transiently ischemic myocardial tissue may increase due to relaxed muscle tone.

Fluorescein fluorescence was found to be an excellent indicator of myocardial perfusion.

Agreement was found between an analytical model for potassium clearance and experimentally determined potassium kinetics. This agreement gave further support to the active clearance process previously suggested by Q_{10} measurements and the slowing of potassium clearance during periods of hypotension.

Publications:

Schuette, W.H., Lewis, D.V. and Vern, B.A.: An Optical Flow Through Technique for Determining Cortical Oxygen Consumption in Cats. In Proceedings of the 28th Annual Conference on Engineering in Medicine and Biology. Arlington, VA, The Alliance for Engineering in Medicine and Biology, 1975, Vol. 17, p. 512.

Vern, B.A., Whitehouse, W.C. and Schuette, W.H.: Sodium-Fluorescein-A New Stable Reference for the Fluorometric Measurement of NADH Changes in the Cat Cerebral Cortex. In Proceedings of the 28th Annual Conference on Engineering in Medicine and Biology. Arlington, VA, The Alliance for Engineering in Medicine and Biology, 1975, Vol. 17, p. 228.

Vern, B.A., Whitehouse, W.C. and Schuette, W.H.: Sodium Fluorescein: A New Reference for NADH Fluorometry. Brain Res. 98: 1-5, 1975.

Lewis, D.V. and Schuette, W.H.: Temperature Dependence of Potassium Clearance in the Central Nervous System. Brain Res. 99: 175-178, 1975.

Schuette, W.H., O'Connor, M., Lewis, D.V. and Van Buren, J.M.: The Design and Operation of a Dual Beam Long Focal Length Fluorometer for Monitoring the Oxidative Metabolism In Vivo. Med. Biol. Engr., March, 235, 238, 1976.

Mutsuga, N., Schuette, W., and Lewis, D.: The Contribution of Local Blood Flow to the Rapid Clearance of Potassium from the Cortical Extracellular Space. Brain Res. 116: 431-436, 1976.

Vern, B., Schuette, W., Whitehouse, W., and Mutsuga, N.: Cortical Oxygen Consumption and NADH Fluorescence During Metrazol Seizures in Normotensive and Hypotensive Cats. Exp. Neurol. 52: 83-99, 1976.

Lewis, D. and Schuette, W.: NADH Fluorescence, $[K^+]_o$ and Oxygen Consumption in the Cat Cerebral Cortex During Direct Cortical Stimulation. Brain Res. 110: 523-535, 1976.

Schuette, W., Vern, B. and Whitehouse, W.: A Low-Light Level Television System for the In Vivo Measurement of Oxidative Metabolism as Indicated by NADH Fluorenscence. Society of Photo-Optical Instrumentation Engineers 89: 47-50, 1976.

Schuette, W., Vern, B. and Whitehouse, W.: A Television Fluorometer for Evaluating Oxidative Metabolism of Exposed Myocardium In Vivo. In Proceedings of the Association for Advancement of Medical Instrumentation 12th Annual Meeting, San Francisco, March 13-17, 1977, p. 50.

Vern, B., Schuette, W. and Thibault, L.: $[K^+]_o$ Clearance in the Cortex. A New Analytical Model. Journal of Neurophysiology (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10023-01 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Two-Dimensional Ultrasonic Imaging System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Electronic Engineer	BEIB DRS
OTHER:	W.S. Friauf	Chief	EEES, BEIB DRS
	T.E. Hall	Electronic Engineer	BEIB DRS
	G.F. Norris	Mech. Engr. Tech.	BEIB DRS
	J.L. Doppman	Chief	DR CC
	T.H. Shawker	Clinical Associate	DR CC
	W.C. Whitehouse	Electronic Technician	ADM CC

COOPERATING UNITS (if any)

DR-CC; ADM-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
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INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several subsystems of a comprehensive, versatile, ultrasonic imaging and recording system were developed. A second generation real-time mechanical sector scanner was completed. A video system for consolidating, displaying, and recording a variety of data was assembled. Considerable progress was made on a solid-state sector to TV scan converter. The subsystems were designed to accommodate subsequent developments in Doppler velocity measurement. The apparatus was applied to ocular, cardiac, and abdominal scanning, and proved to be highly effective for all.

PHS-6040
(Rev. 10-76)

Objectives: Development of a high performance two-dimensional real-time ultrasonic imaging system with provision for Doppler velocity measurements at a selected point and standard TV output to facilitate video tape recording of an examination, including the sector, a view of the patient, real-time clock, additional alpha numeric information, moving trace ECG and pressure data, voice commentary, and audio and/or visual presentation of velocity data. Additional objectives are versatility, that is, suitability for ocular, cardiac, pediatric, and abdominal scanning with minor changes, and high benefit/cost ratio.

Rationale: To be suitable for cardiac usage, among others, a sector scan is virtually essential. While a phased array system is elegant, comparable results can be obtained by mechanically oscillating a single transducer through the desired scan angle. The latter approach has the following advantages: (a) the cost is much lower; (b) no degradation of beam pattern occurs near edges of scan; (c) the single ultrasonic element can easily be changed to provide a resonant frequency which is optimum for the problem at hand and; (d) with only one transducer element, much more sophisticated duplexing, amplification, and signal detection can be achieved at reasonable cost.

Methods Employed: Based on the positive results obtained with the mechanical scanner designed and built earlier, a second generation mechanical sector scanner was developed. The size of the scanner and mechanical vibration have been substantially reduced. In addition, the new scanner maintains electrical control of the scan pattern through the use of position feedback, which provides four major advantages relative to earlier mechanical scanners: (a) a simple control on the console permits instanteous change of scan width; (b) lines are spaced uniformly throughout the sector; (c) synchronization with standard TV systems is easy--a feature which facilitates high-quality imaging in video format; and (d) the instrument can be programmed to execute one or two scans per second, each requiring 1/15 second, with the scanner stopped at the center of the scan the remainder of the time to allow Doppler velocity measurements, guided by the position information. Stopping the scanner most of the time is necessary to get useful signal-to-noise ratio for the Doppler signal.

Major effort was directed to the development of a new device for converting the sector scan to TV video format. Digital storage in solid-state memory will be used, with conversion to and from analog at the output and input, respectively. Compared to present scan converters, the solid state unit will provide a flicker-free display, thus facilitating concurrent spatial and velocity measurements as discussed above. Further, discrete scan lines will not be imaged and other image-processing or image-enhancing procedures can be readily incorporated. Reliability and ease of use should be greatly enhanced.

For the purpose of building up a TV picture with many types of information simultaneously for recording via video tape, appropriate commercial components have been assembled into a system.

Major Findings: It has been found that the new scanner answers virtually all previous objections as to size, weight, vibration, and image quality of mechanical sector scanners.

In abdominal scanning, where it had generally been considered that real-time imaging is unnecessary, it has been found that the real-time feature eliminates image degradation due to motion of body parts and facilitates exploration. The small size of the image near the surface has not been a problem because of the ease of moving the transducer laterally and recording all the information on video tape.

One application of the new scanner was determination of tumor location to facilitate positioning of patients in a whole-body CAT scanner; the CAT scan was being made to evaluate tumor size in cancer patients undergoing hyperthermia treatment, but it was quickly found that tumor size could be determined better with the ultrasonic sector image.

Significance: The main significance is that, through suitable choice of approach, high-quality noninvasive visualization and recording can be achieved at a very reasonable cost.

Proposed Course: Completion of the solid state scan converter is the most urgent immediate objective. Then a major effort will be made to improve image quality by adopting sophisticated techniques from other fields, such as radar and NMR, to allow use of the same transducer for transmission and reception. Concurrently, attempts will be made to incorporate range-gated pulsed Doppler velocity measurement capability at a reasonable cost. Techniques that may eliminate the need for costly high frequency power amplifiers and spectrum analyzers are being explored.

Publications:

Schuette, W., Norris, G. and Doppman, J.: Real Time Two Dimmensional Mechanical Ultrasonic Sector Scanner with Electronic Control of Sector Width. Society of Photo-Optical Instrumentation Engineers 96: 345-348, 1976.

Shawker, T., Schuette, W., Whitehouse, W., and Rifka, S.: An Ultrasonic Real Time Sector Scanner for the Assessment of Early Fetal Development (Work in Progress). In Proceedings of the 2nd International Technology Transfer Workshop on Medical Diagnostic Ultrasound Imaging Technology, Cairo, Egypt, April 1977 (In press).

Shawker, T., Schuette, W., and Whitehouse, W.: Real Time Sector Scanning of Common Abdominal Disease. In Proceedings of the 2nd International Technology Transfer Workshop on Medical Diagnostic Ultrasound Imaging Technology, Cairo, Egypt, April 1977 (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10024-01 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

ELISA Reader

NAMES, [illegible] INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: T.R. Clem Electronic Engineer BEIB DRS

COOPERATING UNITS (if any)

[illegible]

LAB
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☑ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A special-purpose colorimeter is being developed to evaluate the results of ELISA (Ezyme-Linked Immuno Sorbent Assay) tests on small samples. The ELISA test is a simple and safe test for the detection of antibodies and antigens in fluids from human beings. The result of the ELISA test is detectable as an optical density change at a wavelength of either 400 nm or 490 nm, depending on the chemistry of the test. The system allows the chemistry and the final analysis to be performed in the same 96-well microtiter tray, and the sample can be preserved after the test is completed, if desired, for further evaluation. A prototype unit, inexpensive to build and simple to operate, is presently being used.

PHS-6040
(Rev. 10-76)

Objectives: Develop an improved, automated system for immunoassay tests, using the ELISA technique, which does not involve the risks, expense, and inaccuracies of existing tests, to detect selected antigens, and antibodies in fluids from human beings.

Methods Employed: Develop and evaluate colorimetric techniques for the analysis of samples in 96-well microtiter trays of various design and manufacture using an efficient manual positioning technique.

Major Findings: The prototype unit has allowed researchers to develop ELISA methods quicker and with a greater confidence level than was previously possible while allowing them to save their samples for later use.

Significance: This inexpensive, easy-to-use prototype system will allow more rapid development of the ELISA technique, displacing current less accurate, more costly, and more hazardous assay techniques. The further development of a fully automated system will allow large-scale clinical assay tests to be performed quickly and inexpensively, while the small samples required will allow multiple antibody or antigen testing on each patients without requiring an initial large sample.

Proposed Course: Improve the prototype unit to obtain better accuracy and repeatibility; design and develop a fully automated system for handling the sample trays, measuring the optical density, identifying the specimen source, and documenting the results.

Publications:

Yolken, R., Kim, H., Clem, T., Wyatt, R., Kalica, T., Chanock, R. and Kapikian, A.: Enzyme immunoassay (ELISA) for the detection of human reovirus-like agent in human stools. Lancet II: 263-266, 1977.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10025-01 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Blood Gas Analysis Data Acquisition System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.R. Clem	Electronic Engineer	BEIB DRS
OTHER:	G. Vurek	Senior Investigator	LTD NHLBI

COOPERATING UNITS (if any)

LTD-NHLBI

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Biomedical Engineering and Instrumentation

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INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A blood gas analysis data acquisition system is being developed to continuously measure the partial pressure of oxygen and carbon dioxide and the level of oxygen saturation in extracorporeal mammal blood flow in association with a membrane lung. The system is controlled by a microprocessor which commands and acquires data from transducers for pO_2, pCO_2, and O_2 saturation and probe temperature. Values are calculated from these inputs and displayed in units of mmHg pressure and percent of total saturation.

Objectives: Develop an improved, self-contained, automated system for analysis of various gases in continuous, extracorporeal blood flow both as a clinical tool for monitoring patients and as an aid to furthur development of the membrane lung for artificial oxygenation.

Methods Employed: Development of microprocessor-based electronics for control and interpretation of the outputs of recently designed transducers for continuous measurement of O_2 and CO_2 in extracorporeal blood by nonsampling techniques. The use of a microprocessor in the system allows automatic correction for temperature of the probe and input of calibration factors for each transducer in making the pressure calculation. The CO_2 calculation is based on integration of the CO_2 signal, with automatic correction for baseline drift.

Major Findings: The system permits continuous measurement of O_2 and CO_2 content of flowing extracorporeal blood on a routine basis. It allows further evaluation of artificial oxygenation techniques using a membrane lung and may lead to a system that can be used as a clinical tool for continuous monitoring of patients.

Significance: This technique will allow further research in the field of artificial oxygenation to proceed without the encumbrance of the more tedious and less accurate existing methods of measuring blood gas content. This system also allows continuous measurements to be made over an extended time period without the need for periodic sampling of the blood.

Proposed Course: Develop more accurate calculations from the input information, provide more functions as the need and desirability for them arises, and reduce the size and complexity of the overall system as new microprocessor components become available.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10026-01 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Microprocessor-Based Biomedical Instrumentation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.C. Gibson	Electronic Engineer	BEIB DRS
OTHER:	R.L. Berger	Senior Investigator	LTD NHLBI
	R.M. Winslow	Senior Investigator	CHB NHLBI

COOPERATING UNITS (if any)

LTD-NHLBI, CHB-NHLBI, LBS-NICHD

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Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Microprocessor-based biomedical instrumentation introduces features not possible with previous types of units. The instruments are able to control an experiment do calculations on the data, and make decisions based on the results. The advantages to the researcher are that he can do experiments not possible before and measure results as they occur. We have built several such instruments, all designed for laboratory use. The oxygen equilibrium curve analyser allows a relatively unskilled technician to generate 10 to 12 oxygen equilibrium curves a day on whole blood. The results are displayed, plotted, and stored for future use. The instrument is being used to determine the significance of shifts in oxygen affinity in human blood. The microcalorimeter heat correction unit converts a voltage into a heat of reaction in real time. The unit also does baseline correction and computes the rate of change of heat of reaction at selected times. The data is printed, displayed, and stored for future use. The temperature probe uses a microprocessor to linearize a thermistor over a range of 100° C with an absolute accuracy of 0.001°C.

Methods Employed: Microprocessors, together with associated devices such as analog-to-digital converters, memories and keyboards, plus software, have been utilized to replace conbinations of conventional electronic equipment and digital computers. The powerful data processing and control capabilities of the microprocessor have been exploited to provide automatic zero as well as calibration, linearization and interactive entry of constants and other sophisticated features not practical heretofore.

Major Findings: Microprocessor-based instruments can provide improved performance, greater convenience (because all data processing functions are performed immediately and without the need of dealing with a computer separately) and savings in instrument cost and computer charges. Duplication and modification of prototypes are simplified because much of the complexity is in software.

Publications:

Winslow, R.M., Morrissey, J.M., Gibson, C.C. and Berger, R.L.: Variability of Oxygen Affinity of Normal Blood: An Automated Method of Measurement. J. Appl. Physiol. (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10027-01 BEI

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Development of Whole Body Hyperthermia Instrumentation and Control System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Electronic Engineer	BEIB DRS
OTHER:	J. Bull	Senior Investigator	MC DCT NCI
	R. Atkinson	Special Project Officer	OD DCT NCI
	D. Lees	Staff Anesthesia	CC NIH
	J. Whang Peng	Senior Investigator	MS DCT NCI
	R. Corsey	Electronic Engineer	BEIB DRS

COOPERATING UNITS (if any)

MB-DCT-NCI; OD-DCT-NCI; CC-NIH; MS-DCT-NCI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Whole body hyperthermia is being studied at NIH as a possible means of treatment for cancer. This project includes the development of an instrumentation and control system based on the utilization of a Tektronix 31 programmable calculator, with a digital plotter and interface for data acquisition and temperature control of the hyperthermia device. A Webb Associate Hyperthermia machine has been modified for direct computer control in order to simplify system operation.

PHS-6040
(Rev. 10-76)

Methods Employed: A Tektronix 31 programmable calculator is being used to acquire, record and process data as well as to control water temperature of a Webb Associate Hyperthermia Suit. The temperature of the water pumped through the suit along with esophageal and rectal temperatures of the patient are processed by the calculator, which then develops temperature commands for the water temperature mixing valve. The mixing valve adds hot or cold water to that returning from the suit as directed by the calculator. A sixteen-channel analog multiplexer was designed to plug into the Tektronix digital interface unit so that heart rate, blood pressure, and temperature data could be processed by the system. The multiplexer module also provides commands from the calculator to the water mixing valve motor. Automatic cool-downs are programmed into the calculator in response to various out-of-limit conditions. The calculator functions in an interactive mode for entry of operational instructions.

Major Findings: The major finding from the use of the equipment is that it is possible to take the whole body core temperature of patients to $42.0 \pm 0.1^{\circ}C$ for four hours on a biweekly basis without major difficulty. The finding suggests that hyperthermia treatment for persons with cancer may be practical.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10015-02 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Development of Miniature Catheters for Clinical Use

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	J.L. Doppman	Chief	DR CC
	J.W. Boretos	Physical Scientist	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this work is to develop miniature catheters for insertion into tortuous blood vessels as small as 1 mm diameter and up to 15 cm long. Techniques of delivering embolizing materials will be developed so that procedures previously requiring surgery can be performed instead with catheters. Topographic catheter and other novel concepts are being explored for this task.

PHS-6040
(Rev. 10-76)

Objectives: Develop techniques and devices for inserting a miniature catheter into small tortuous vessels.

Develop techniques and devices for delivering therapeutic materials into the catheterized vessel.

Methods Employed: A miniature topographic catheter is being developed.

Major Findings: It is possible to develop a miniature topographic catheter. The device is capable of negotiating tortuous paths *in vitro*.

Significance: Surgeons and radiologists have long sought techniques for catheterizing small diametr vessels separated from larger, easily catheterized vessels by long, narrow passages with numerous bifurcations. The capability would permit selective treatment of tumors, aneurysms and other lesions without danger to normal tissues.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10021-02 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Development of an In Vivo Micro Spectrophotofluorometer for Use in Laboratory Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	P.M. Gullino	Chief	LPP NCI
	F.H. Grantham	Associate	LPP NCI
	P.M. Bungay	Chemical Engineer	BEIB DRS
	R. Bonner	Physicist	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop the technology and methodology to perform micro spectrophotofluorometry in caged laboratory animals using miniature fiber optic probes. The technique will be used initially for microwashout studies of tumors in rats using intravenously injected fluorescein to investigate variations in tissue perfusion in the tumors. In the future, we hope to employ the technique to study metabolic behavior of tumors and pharmacokinetics in animals.

PHS-6040
(Rev. 10-76)

Objectives: (1) To develop the technology and methodology required to make chronic in vivo fluorescence measurements in caged rats.

(2) Study the distribution and variation of local tissue perfusion in tumors implanted in rats.

(3) Extend the technique to study tissue metabolism under controlled conditions.

(4) Extend the technique to perform pharmacokinetic studies in animals.

Methods Employed: Pairs of single fiber optic strands are implanted along with tumor fragments in a rat. One fiber in each pair goes to a high-intensity light source; the other fiber of each pair goes to a multiplexed high-gain photomultiplier tube. Fluorescent dye injected into the cardiovascular system diffuses into the interstitial fluid of the tumor, is illuminated, fluoresces, and is eventually washed out. The time course of the fluorescence signal is then related to local tissue perfusion and other factors contributing to transport within the tumor.

Major Findings: A new system based upon the original preliminary test apparatus has been designed, built and tested and is presently being checked out in animals.

Significance: Development of this technique will allow in vivo localized measurements in animals, not previously possible, on a continuing basis. A great variety of experiments involving blood flow, metabolism, and pharmacokinetics will become possible, which could enhance understanding of transport and metabolism in tumors and normal tissues.

Proposed Course: Complete the animal checkout, carefully examine the light phenomena occurring in the tissue at the probe tip, carefully quantitate the relationship between dye concentration and fluorescence, perform animal measurements, if desirable, develop a computer interface for data processing, and extend device to related types of measurements.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10016-02 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Differential pH/Thermal Titration Apparatus

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	BEIB DRS
OTHER:	R. Berger	Senior Investigator	LTD NHLBI

COOPERATING UNITS (if any)

LTD-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.2	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underling keywords)

A differential pH/thermal titration apparatus has been developed which permits the study of small and rapid temperature changes associated with the exothermic heats of reaction of acid or base titration of protein solutions. Simultaneous measurement is made of the associated pH changes. Two reaction cells are maintained at constant temperatures (.005° C drift in 2000 seconds) in a common heat exchanger. Acid or base is delivered at a constant rate and rapid mixing is accomplished with a constant-speed (±.5%) stirring system. pH and temperature changes are recorded on a single cell or differential basis.

Objectives: To develop a system which permits study of acid/base titrations of protein solutions on a differential basis with high resolution and rapid response.

Methods Employed: Equipment has been designed consisting of a constant-temperature differential reaction cell, a constant-speed titration system, a constant-speed mixer and a rapid-response pH electrode and thermistor.

Significance: The equipment permits calorimetric study of the chemical kinetics of protein solutions.

Proposed Course: To develop a rapid-temperature equilibration system.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10028-01 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

An Analytical Model for the Structural Response of Intracranial Contents to Systemic Arterial Pressure

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	BEIB DRS
OTHER:	D Sobel	Mechanical Engineer	BEIB DRS
	A. Lee	Mechanical Engr. Technician	BEIB DRS
	C. Li	Associate Neurosurgeon	

COOPERATING UNITS (if any)
SN-NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

It is believed that the mechanical properties of the intracranial contents change with different pathologic conditions. For example, the compliance of the brain decreases with edema. In order to provide clinical information relating to such phenomena, an analytical model is under development. In the model, the system arterial waveform is treated as a forcing function for a structural model of the intracranial contents. The response of the system is considered to be manifested in the dynamic intracranial pressure measurement. The model will be tested on healthy monkeys and then applied to a variety of well-defined pathologic conditions.

PHS-6040
(Rev. 10-76)

Objectives: To provide an analytical model which relates systemic arterial pressure and dynamic intracranial pressure as a function of a number of pathologic conditions.

Methods Employed: Experimental measurements of intracranial pressure are being made epidurally with a custom-built solid-state pressure transducer, and a computer model of the structural response is being developed.

Major Findings: The solid-state pressure transducer is providing good dynamic response and can accurately detect arterial pressure pulsations and respiratory effects on the intracranial pressure waveform.

Significance: The model could lead to development of equipment that would provide feedback to the physician for assessing the efficacy of treatment.

Proposed Course: To test the model in healthy and sick animals.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10029-01 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Modulation of Transendothelial Mass Transport by Hydrodynamically Induced Steady and Unsteady Wall Shear Stress

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	BEIB DRS
OTHER:	R. Dedrick	Chief	ChES BEIB DRS
	D. Fry	Chief	IR EA NHLBI

COOPERATING UNITS (if any)

IR-EA-NHLBI

LAB/BRANCH
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Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Analytical and experimental studies are underway to investigate the relationship between hemodynamic events and alterations in the arterial endothelial permeability for macromolecules. An apparatus has been developed to produce a well defined shear stress field over a segment of isolated arterial tissue. The shear stress field has been studied analytically, and experiments utilizing the electrochemical technique for the measurement of shear stress are in progress to attempt to validate the analysis. Permeability studies using radioactive tracer material and albumin labeled with Evans Blue Dye will begin on dog aorta after validation has been completed. Both steady and unsteady shear fields will be studied.

PHS-6040
(Rev. 10-76)

Objectives: It is believed that mechanical factors play a role in the atherosclerotic process. Local hemodynamic events produce forces which cause the aortic wall to be stressed. This study has been undertaken in an attempt to isolate one of those stresses, namely the hydrodynamically induced wall shear stress.

Methods Employed: An analytical solution for the shear field in a fluid rotating in a region at the ends of concentric finite cycliners has been obtained. The electrochemical technique for the measure of shear stress is being used to validate the analysis.

Major Findings: Further testing of the physical model is necessary in order to validate the fluid mechanical analysis. The electrochemical technique is highly sensitive to the diameter of the electrode (D^2) and to the concentration of the potassium ferricyanide (C^3); methods of measurement must be precise.

Significance: In order to study the influence of a variety of mechanical factors and their role in the atherosclerotic process, factors must be studies in isolation. Our methods isolate for study the steady and unsteady wall shear stress effects on the modulation of endothelial permeability.

Proposed Course: To validate the analytical model and then apply the technique using aortic endothelium from the dog in order to relate changes in permeability to hydrodynamically induced shear stress.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10030-01 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)
Effects of Mechanical Stress on Proliferation and Morphological Development of Bone Cells in Culture

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	BEIB DRS
OTHER:	I. Binderman	Visiting Scientist	LDBA NIDR

COOPERATING UNITS (if any)
NIDR

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.3	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The proliferation and morphological development of bone is known to be influenced by mechanical forces. A system has been developed to study the effects of mechanical stress on cells in tissue culture. The cells under study are cultured on polyether polyurethane or silicone rubber membranes. The membranes are then deformed by uniform hydrostatic pressure. Analysis of the membrane is made to determine the strain imparted to the cells. The pressure applied to the membrane is controlled by a fluidic control circuit which allows the investigator to vary the magnitude and time-varying nature of the strain imparted to the cells. A time-varying strain is employed because of the viscoelastic character of biological tissue.

PHS-6040
(Rev. 10-76)

Objectives: To study the effects of cyclic loading of biological tissue in culture. To investigate the effects of mechanical stress on cell proliferation and on their morphological development.

Methods Employed: An analytical study of the stress field in a clamped membrane under load by a uniform hydrostatic pressure is being performed by finite element methods.

A fluidic control circuit using gas from the tissue culture incubator to power the system has been developed.

Major Findings: Cells undergoing cyclic variations during mechanical stress appear to align in a preferential direction when compared to controls which are not stressed. The direction or orientation may correspond to the radial component of the stress field.

Significance: The system permits the investigator to apply carefully controlled levels of stress to a variety of cell types in an attempt to elucidate the relationship between mechanical stress and concomitant biological processes.

Proposed Course: To provide instrumentation to monitor biochemical processes occurring as a function of mechanical stress. To provide analytical services associated with studying the effects of mechanical stress on membrane permeability in biological tissue.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10031-01 BEI

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Multimode Visual Display

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS
OTHER:	E. Walker	Mechanical Engineer	BEIB DRS
	D. Reingold	Research Associate (IPA)	CB NEI

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.3	0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A servo-controlled, two-axis visual target project, rotating optokinetic panoramic display, and integrated spherical projection screen is being developed. Preliminary design is complete, and final design is well underway. The system will permit studies of visual tracking functions and visual-vestibular interactions.

PHS-6040
(Rev. 10-76)

Objectives: (1) To facilitate experiments concerned with control of eye movements and visual functions. (2) To permit experiments to be made with healthy human beings and patients with a variety of neurological disorders. (3) To permit precise and convenient measurements under computer control of visual and visual-vestibular interaction.

Methods Employed: The patient will be seated with his head at the center of a six-foot diameter spherical projection screen. A wide-angle lens and a projector system placed above the sphere provide a panoramic display on the interior surface of the sphere; a motor-driven slide in the projection system can create a rotating display. A separate projection system just above the patient's head consists of a long focal-length optical device and a mirror privoted about two axes. The mirror is driven by two high-performance D.C. servomotors controlled by the computer. The second projection system will permit a small target (up to 2^{o}) to be moved rapidly on the screen to study visual tracking by the subject. A variety of slides can automatically be put in position in either projection system. Eventually the orientation or tilt of these images will also be under computer control.

Major Findings: The major parts of the system have been designed and are currently being built.

Significance: Development of the instrument will allow investigators in the National Eye Institute to conduct a variety of experiments on visual and visual-vestibular interactions. The position and velocity of various moving spots of light will be programmable, and experimental paradigms can be stored on a computer and called up when required.

Proposed Course: As fabrication proceeds, the system will be assembled, checked out, and debugged. The system will then be interfaced with the computer and tested further.

DIVISION OF RESEARCH SERVICES

Summary of Program Activities July 1, 1976, through September 30, 1977

ENVIRONMENTAL HEALTH AND SAFETY PROGRAM

Dr. Rudolf G. Wanner
Associate Director

I. SUMMARY

Coordination and central management of the Environmental Health and Safety Program activities was further consolidated during the reporting period. The two operating units of the program, the Environmental Safety Branch and the Radiation Safety Branch, received administrative and managerial support to allow for general intensification of all functions, with emphasis on meeting the needs of rapidly evolving research, such as recombinant DNA molecule studies.

During the year, two additional employee groups were included in the medical surveillance program. A considerable increase in responsibilities ensued from new NIH policies and also from federal regulations, including the National Environmental Policy Act and the Occupational Safety and Health Act. We prepared a number of environmental documents for NEPA and continued to develop and distribute training materials as well as administer training programs, in the fields of radiation safety, biohazard control, laboratory safety and occupational health.

Special investigations of laboratory incidents and accidents were conducted and the findings disseminated throughout the biomedical research community with recommendations for prevention. As the use of radioactive materials in research and diagnostic procedures continued to grow at NIH, radiation safety activities were expanded to meet the needs of the intramural staff and the requirements of the Nuclear Regulatory Commission.

ENVIRONMENTAL SAFETY BRANCH — VINSON R. OVIATT, CHIEF

The Environmental Safety Branch (ESB) is carrying out numerous responsibilities regarding research with recombinant desoxyribonucleic acid (DNA) molecules and chemical carcinogens. Whereas some of the projects are designed to meet NIH requirements, other duties are consequent to federal legislation controlling toxic substances. The related work done by our staff will be set forth with relevant detail in subsequent sections of this report.

ESB participated in two international biohazard control programs. It planned and sponsored the World Health Organization/National Institutes of Health (WHO/NIH) Consultations on Facilitation and Safety in International Transfer of Research Materials held in Geneva, Switzerland. The conference organized the WHO Programme on Safety in Microbiology and four related Working Groups. Staff took part in the National Institutes of Health/European Molecular Biology Organization (NIH/EMBO) Consultations on Laboratory Design in London, England, which resolved design discrepancies between the U.S. and European nations.

Control of the laboratory use of chemical carcinogens involved participation with the Department of Health, Education and Welfare (DHEW), the National Cancer Institute (NCI), the Environmental Protection Agency (EPA) and related professional societies in developing operational guidelines and design standards. Work began on compiling an ongoing inventory of chemical carcinogens in use at NIH. Procedures were instituted to govern the disposal of chemical carcinogens and toxic chemicals at NIH. A research project is underway to improve methods for disposal of the waste chemicals.

Additions to the safety management staff permitted an increase in accident investigation activities. A planning and evaluation team was organized to develop and carry out a safety inspection program for NIH work places. The DHEW Safety Office audited the NIH program and identified areas for improvement. The suggestions are bing pursued.

Training endeavors focused mainly on the development of educational materials and manuals, which include four slide/cassette programs, Chemical Hazard Data Bulletins, the Environmental Health and Safety Report, a new series of safety posters, a chemical safety guide and a compressed and liquified gases program and guide. A contract was initiated for the preparation of a programmed instruction course in "Fundamentals of Laboratory Safety." Training in biohazard control programs was provided to 124 investigators, and 2 series of courses in chemical safety practices were offered to NIH investigators.

Continuing Branch programs which required considerable attention were those associated with solid waste collection and disposal, provision of high-purity water, and media production.

A. Current Programs: Progress and Accomplishments

1. Administration and Environmental Analysis

This program encompasses the activities of the Office of the Branch Chief, including usual administrative affairs, support of National Environmental Policy Act activities and serving as Executive Secretariat of the NIH Biohazards Committee. The Branch has not previously reported the activities of the Office of the Chief as a program. The step is being taken because the Chief and his assistant expended the equivalent of 1½ man-years on professional services other than general Branch administration.

Tasks related to the National Environmental Policy Act constituted a significant part of the workload. Highlights were:

*A draft of an Environmental Impact Statement was prepared by NIH for the Guidelines for Research Involving Recombinant DNA Molecules. Toward this effort, ESB provided consultation on the scope, content and distribution of the draft. About 3,000 copies have been distributed. ESB helped review comments on the draft and prepare the final Environmental Impact Statement.

*An environmental analysis of all NIH programs was undertaken. The analysis will not be completed during this fiscal year.

*Consultation was provided to the Lister Hill Center for Biomedical Communications on an environmental analysis of their Earth Station and Communication Technology Satellite project.

*Environmental analyses of two high-risk containment facilities were conducted, one for the NIH Mobile Containment Laboratory and the other at the Frederick Cancer Research Center (FCRC), Frederick, Maryland.

*Determinations of Inapplicability prepared by the Division of Engineering Services for NIH construction activities were reviewed:

Radiation Oncology Facility, Building 10
Southwest Segment of Circumferential Loop Road System
Building 38A and Multilevel Parking (MLP) - 7A
Building 10B, Ambulatory Care Research Facility (ACRF) and MLP 1A and 5
Building 34A
Modifications to Wastewater Treatment Plant, the National Institutes of Health Animal Center (NIHAC)
Licensing of 140 acres from U.S. Navy, Caribbean Primate Research Center, Puerto Rico

Intramural research activities related to DNA recombinant molecule research has significantly escalated the workload associated with the Secretariat of the NIH Biohazards Committee. Thirty-two Memoranda of Understanding and Agreement pertaining to this research were processed. This activity involves appointing and administering the work of special study committees and

coordination with the involved institutes, the Office of Recombinant DNA Activities in the National Institute of General Medical Science and the Deputy Director for Science. The added workload particularly affects the secretarial staff as it entails at least one-half person years' stenographic work.

The staff participated in the NIH/EMBO Consultations on Laboratory Design and Safety Practices held in London, England, March 1977. The conference developed standard laboratory design concepts and safety procedures appropriate to DNA recombinant molecule research and resolved differences in U.S. and European standards and practices.

The Branch initiated and funded the WHO/NIH Consultations on Facilitation and Safety in International Transfer of Research Materials, which were held September 14-17, 1976, in Geneva, Switzerland. The consultations resulted in formation of a WHO Programme on Safety in Microbiology. Four WHO Working Groups were formed: Transportation, Emergency Services, Laboratory Safety Elements and Maximum Containment Facilities. Branch staff serve on the Executive Directorate of the Programme and as Chairperson of the Working Group on Laboratory Safety Elements.

A conference on "Environmental Health and Safety Requirements for Sponsored Research in Higher Education" was held by ESB at NIH in cooperation with the American College Health Association. The objective of the conference was to acquaint persons responsible for research administration and environmental health and safety efforts on university campuses with health and safety guidelines to be followed in the conduct of federally-sponsored research. The conference was attended by 158 college administrators and health officials.

2. Biohazards and Contamination Control

The biohazards and contamination control program is designed to promote a safe environment for personnel and to protect research work at all NIH facilities in Bethesda and in the field. Potentially hazardous laboratories, animal areas and control equipment are inspected regularly. Consultation is provided on a case-by-case basis to provide laboratory arrangements that protect the investigator and the public.

A large workload resulted from increased emphasis on research involving recombinant DNA molecules at NIH. For half of the year, two staff members have been assigned full time to coordinate renovations and provide final certification of two P-4 (high containment laboratory) facilities--the Mobile Containment Laboratory at NIH and Building 550 Class III Biological Containment System at the FCRC. These concurrent projects have required over 300 man-days of ESB time. Also, 26 P-1 (minimal containment), P-2 (low containment) and P-3 (moderate containment) laboratories were certified.

The Branch entered into a Loan of Equipment Agreement with the National Sanitation Foundation. All necessary equipment for testing Class II Bio-

hazard Cabinetry in accordance with NSF Standard No. 49 was provided to assist NSF in implementing the testing and listing of approved equipment.

Approximately 1,000 copies of the NIH Biohazards Safety Guide were distributed to interested individuals outside NIH; 100 copies were distributed to NIH investigators. The quarterly memorandum, "Biological Laboratory Hazards" was distributed to more than 260 laboratories, including several overseas institutions.

Consultations with individuals at NIH and outside NIH on equipment, safety devices and recombinant DNA are shown in the following table (each consultation required an average of four hours).

	NIH	Outside NIH
a. Selection of equipment	60	20
b. Proper use of equipment	15	0
c. Safety devices and biohazards control	110	30
d. Recombinant DNA	46	4

Whereas 55 new Class II biological safety cabinets were installed at NIH and 18 were provided to NIH investigators as part of the ESB Emergency Issuance Program, an additional 102 were ordered; 430 safety cabinets were tested under contract to ensure that operator protection was provided. A total of 104 equipment requisitions was reviewed and approved. Building exhaust system filters, vacuum system filters and sterilizers in biohazardous containment areas were tested and repaired as needed.

The 17 plan reviews of major laboratory renovations included projects in the Open Bay Area of Building 41, Buildings 5, 6, 6A, 8, 10, 14E, 29, 29A and the ACRF. Recommendations were made to the Director of the Division of General Services of the Alcohol, Drug Abuse and Mental Health Administration on decontamination of laboratory space to be occupied by his staff. The building was previously used for work with oncogenic viruses.

A total of 6,482 bacteriological tests was performed in the analysis of patient food and milk, potable water, waste water, and other environmental samples. A survey of the de-ionized water units in the chemistry section of Clinical Pathology was conducted to determine bacterial quality.

A survey was made to determine the levels of mold spores in the air supply of Building 37. Although no excessive levels of mold spores or viable bacteria were detected, Room 2A23 continued to show high levels of mold spore contamination during the year. The source is associated with the high-humidity incubators. A special antifungal spray, employed to correct a similar problem in Building 5, will be used on the four incubators in 2A23, and studies of the air contamination will be continued.

3. Industrial Hygiene

The industrial hygiene program detects, evaluates and controls environmental factors and stresses which may cause illness or significant discomfort among

workers or members of the community. Laboratory use of chemical carcinogens and gaseous and particulate air contamination potentially or actually generated at NIH are of particular concern. Problems of noise, temperature extremes, and non-ionizing radiation are also investigated and resolved.

Staff involvement in the control of chemical carcinogens at NIH continues at a high level. Activities include participation in the duties of the Chemical Carcinogen Safety Standards Subcommittee of DHEW and technical support to NCI for the control of chemical carcinogens in intramural and extramural programs. Work has also been undertaken to compile an ongoing inventory of chemical carcinogens in use at NIH, which will provide more positive control over the distribution and handling of the chemicals.

The NIH chemical fume hood surveillance program was completed by contract in July 1977. Of 793 checked, 125 were found to be below the minimum acceptable standard; 346 are operating at less than a 12-inch sash height. Corrective actions have been initiated where substandard hoods pose a handicap to investigators. Followup hood evaluations were made by ESB throughout the year.

Intensive investigation of environmental conditions affecting employee health and research efforts for NCI in Building 37 was initiated by ESB. Factors investigated included the building's exhaust system, re-entry of rooftop exhaust gases and vapors, air supply, incubation and media contamination, waste handling, housekeeping procedures and ventilation and plumbing cross connections.

Approximately 20 noise complaints at NIH were investigated this year. The complaints came from laboratories, offices, shops, the tunnel and rental facilities. Corrective measures included modifications to limit the source of excessive noise, relocation of personnel and the provision of hearing protection.

Chemical spills continued to plague the research environment. Related to these spills, advice was given concerning exposure and toxicity hazards, explosion potentials, and handling and disposal alternatives.

More than 150 odor complaints were investigated. Problems ranged from the improper storage and disposal of dead animals and other putrescible waste to problems with plumbing and ventilation systems. Improper handling and disposal of chemicals, as well as chemical spills, accounted for a significant portion of these complaints. The most far-reaching episode of the year centered around the accidental release of 2-mercapto-ethanol to the NIH sewer system. Odor complaints were received all the way from Building 37 where the chemical was discharged, to Building 21, the last occupied workplace on the NIH sewer line. The episode graphically points out the need for tight control over disposal of waste chemicals.

Environmental and industrial hygiene evaluations were conducted on Buildings 4 and 21. Numerous hazardous and potentially hazardous situations were found in Building 4; those conditions were described, along with recommendations for correction, in a report to the management of the building. Building 21, by contrast, was found to be a good model for correct health and safety conditions.

4. Hospital Environmental Control

ESB participates in the Clinical Center Multidisciplinary Safety Committee and in projects designed to protect patients, employees and visitors from environmental influences that may be unsafe, unhealthful or uncomfortable. Program liaison is provided through monthly planning conferences with hospital officials.

Branch staff has been active in the construction program of the ACRF addition to the Clinical Center. Planning assistance has been provided for proposed environmental systems. Current activities relate to minimization of environmental and safety conditions unfavorable for patients, staff and research during construction activities.

ESB reviewed plans and participated in the selection of equipment for the renovation and modernization of the floor kitchens and the main food preparation area of the Clinical Center patient care facility. Environmental inspections were made of 22 nursing units. Operating room surveys were conducted in December, April and August.

5. General Sanitation and Sanitary Engineering

The general sanitation and sanitary engineering program is concerned with basic environmental factors affecting the health of NIH employees. The community and visitors and the quality of the research environment. The factors include food sanitation, water supply, solid and liquid waste disposal, housekeeping practices, pesticides, water pollution control and handling and disposal of waste chemicals.

A major endeavor was made to improve methods for disposal of waste chemicals. Five thermal destructors that show potential merit have been identified, and a contract is currently being executed to do on-site testing of the units. If one or more of the test units proves to be suitable, it will be recommended that NIH procure a unit for use on campus. Significant interest in this project has been shown from research facilities throughout the country.

Three Instruction and Information Memoranda (Nos. 76-2, 77-1, and 77-2) were issued this fiscal year to simplify the transition to new handling procedures for solid wastes being established at NIH. Also, a previous memo concerning carcinogen handling and disposal has been modified and updated and is being redistributed as a Manual Issuance (3032-2).

Work continued on the animal room surveillance program with major emphasis on upgrading equipment for washing cages and racks and improving room ventilation. Some washing machines have been replaced and others are scheduled to undergo major renovations.

Metal garbage cans are being replaced by disposal containers for solid wastes at NIH. ESB is carrying the major workload in the conversion to paperbags and cardboard boxes. An automated conveyor system and incinerator have been installed and are in use.

A waste chute disposal system for Building 10 is being installed and will be in operation next year. ESB is participating in the design, selection and installation of the equipment.

A new snack bar operated by the Blind Industries and Services of Maryland has been built and is in operation in Building 12B. ESB participated in the design of the snack bar and selection and installation of the equipment and, also, inspected the facility before it was opened.

High-purity water production remains a priority program. Routing specific resistance measurements and annual copper analyses of the central distilled water systems were completed. To date, 28 investigators have received one ore more of the high-purity water glass stills developed by ESB; 16 additional units are pending.

Routine monitoring of NIH and NIHAC water systems continued throughout the year. The severe winter created some freezeup problems with the automated samplers located adjacent to Broad Run Creek. We hope burial of the monitor's intake lines has eliminated the problem.

ESB reviewed regulations for the NIH Agency Environmental Officer. The newly enacted "Toxic Substances Control Act" and "Resource Conservation and Recovery Act" may have significant impact on our waste handling systems.

6. Safety Management

The goals of the safety management program are to prevent accidents and provide professional services required for development, coordination and implementation of occupational safety and health standards. It provides an accident-reporting investigation and analysis service, conducts a Branch training program and administers the Federal Employees Compensation Act for NIH employees. The program was fully staffed for the first time in several years.

DHEW and PHS Safety Officers recently conducted an in-depth evaluation of the NIH Safety program. While generally complimentary, the inspectors made several helpful suggestions, including: (a) establish and NIH Safety Committee; (b) develop an NIH Safety Policy; (c) centralize codes and standards; and (d) formalize many "informal" NIH procedures and policies. The recommendations are receiving current attention.

The NIH system for reporting and analyzing accidents was recognized as highly effective and accurate by DHEW. The program's analytical capacity has been used to identify and highlight specific problem areas.

With the advent of a full staff, accident investigations activities were measurably increased. In addition to obtaining more precise data, our staff has additional opportunities to deal directly with specific safety needs in the various work areas and increased personal contact throughout NIH.

A planning and evaluation team was organized to develop an ESB safety inspection program for NIH buildings. Early experience with the program indicates that it will reduce accident potentials.

In coordination with Materiel Management, requirements for improved protection of chemical containers were established. The action grew out of an accident resulting in a serious acid burn to a National Institute of Mental Health employee. A videotape was prepared on the tests conducted by the Branch on chemical bottles coated with polyvinyl chloride.

The compensation office continues to receive a high number of claims associated with the provision that permits continuing an employee in a pay status up to 45 days when absenteeism results from work-related injury. There is increasing success in encouraging supervisors to contravert questionable claims and, while it is too early to clearly identify a specific trent, it appears that the Department of Labor is supporting our efforts. While these efforts are reducing loss of time and costs associated with accidents, they have added a significant amount to the overall workload.

7. Media Production

The media production program maintains, propagates and produces in large volumes a variety of continuous cell-line tissue cultures to supply NIH requirements not met by commercial sources or individual laboratories. Media for the culture of bacteria, fungi and tissue cultures are produced. The program also freezes and stores valuable cell lines for long-term preservation.

Projected workload figures for the reporting period show 18,750 requisitions for bacteriologic and tissue culture media, totaling 186,000 liters of media, were processed. Of the total, 95,000 liters were tissue culture media and 91,000 liters were bacteriologic media. The production of more tissue culture media than bacteriologic media ia a reversal of the trend noted over the last two years.

Issues of blood agar plates of all types totaled 187,000 for the reporting period. An additional 552,000 plates of other types resulted in a total plate production of 739,000.

Issues of tissue culture cells as cell suspension remained at the same level as last year, with a total of 125 liters of suspension produced. Tissue culture cell freezing and storage services remained at the same level with a total of 2,500 ampoules of cells frozen, and over 4,000 ampoules of cells maintained in the frozen cell bank.

8. Glassware Production

The glassware production program decontaminates, sorts, cleans, inspects, prepares and reissues laboratory glassware to NIH investigators throughout the campus. It also furnishes cage-washing services to the Clinical Center. Another service is the provision of ethylene oxide sterilization of heat labile equipment used in laboratories and for patient care.

Glassware issues projected for the 15-month reporting period total 9,561,000 pieces, a slight decrease over last year. In addition, 371,000 cages, racks and associated pieces of equipment were processed.

Environmental improvements in the glassware and cage-washing ares to provide an improved air handling system, better lighting and more efficient and pleasant sorting and inspection areas are about 80 percent complete. Without the improvements, it would be impossible to work in this area due to the ACRF construction and its attendant dust and noise problems.

To replace stainless stell trays for return of dirty glassware, 600 plastic trays were put into circulation this year. Acceptance by the NIH investigators has been good, and resistance to daily wear and tear under routine conditions has been satisfactory.

Issues of unplugged, nonsterile culture tubes, when requested, are now being made in a factory package supplied by the manufacturer. The method has been well received by investigators and makes valuable man-hour available for other types of production.

Changes in the policy regarding dirty glassware at the Clinical Center, requiring the investigator to return only recycled glassware, has eliminated the handling of disposable material and improved the return of reusable glassware.

9. Environmental Studies for Support of Research and Patient Care

Continuing environmental studies are conducted as a necessary adjunct to surveillance and consultation activities. Studies include evaluation of new equipment and methods, production of quality glassware and high-purity water, identification of environmental contaminants and assessment of environmental stresses related to light, heat, noise, food, water and waste.

A bioassay of Broad Run, the stream passing through the NIHAC property, was completed. This data is the last required to determine the effects of the present NIHAC sewage treatment plant on that creek. It will provide baseline environmental data for the projected sewage treatment modifications.

A study was completed identifying emergency water supplies for the patient area of the Clinical Center. In conjunction with this study, two NIH wells were analyzed, under contract, with respect to new EPA drinking water standards. The wells will be suitable for this use if a chlorination system is added to eliminate bacterial contamination.

Another study was made under contract of NIHAC's well water and waste water effluent to ascertain if significant detrimental chemical pollution was occurring. Two such pollutants were found and subsequently eliminated from use at NIH. Followup testing confirmed their removal.

The services of a professional sanitary engineer were enlisted to assist in formulating test procedures for analyzing NIH sewage for significant chemical pollution. A list of parameters and a sampling format was developed.

Studies of disinfectants used in the Clinical Center indicate that the newer types of quaternaries are at least as effective as the phenolics and have a lower toxicity factor in sewage disposal.

A collaborative study of surgical handwashing procedures was conducted with the animal operating room staff of the Veterinary Resources Branch of this Division. Results indicate that new germicidal foam preparations are more effective and simpler to use than extended, traditional handwashing.

10. Training

Training to promote job effectiveness is provided for ESB personnel and staff members at NIH. The training is particularly related to the special environmental control devices and practices required in research areas.

The slide/cassette program, "Introduction to Biohazards Control," was completed. Work was initiated on a similar presentation on "Safe Handling of Lab Glassware." Contract work was completed on both a Senior Federal Official Safety Briefing and the NIH Guidelines for Recombinant DNA Molecules. Production of the latter program is being delayed pending changes now under consideration by NIH.

Chemical Hazard Data Bulletins on 20 chemicals were prepared during the year. The "Environmental Health and Safety Report" was prepared and distributed periodically. A new series of safety posters was initiated.

Work was begun on a "Chemical Safety Guide" and the revision of the existing "Compressed and Liquified Gases Program and Guide." A contract was initiated for preparation of a programmed instruction course in "Fundamentals of Laboratory Safety."

The slide/cassette training programs on "Effective Use of the Laminar Flow Biological Safety Cabinet," "Assessment of Risk in the Cancer Virus Laboratory" and "Hazard Control in the Animal Laboratory" were shown to 124 investigators. Two series of courses were offered to NIH intramural investigators on the safe handling and use of laboratory chemicals. The first course, presented four times, was an orientation to safe procedures and practices. The second course consisted of 10 hours of instruction of the fundamentals of laboratory safety, development of safety procedures and the training of laboratory staff.

On-the-job training was provided to three students in environmental health, one in safety management, one in virology and on in the National Science Foundation High Achievement Program.

Staff presented papers at the American Society for Microbiology, the 19th Biological Safety Conference, the American Hospital Association Conference on Anesthetic Gases and other professional meetings. Staff served as faculty members at the University of Maryland and George Washington University.

ESB staff received 2,069 hours of training at designated short courses or in college and university classes.

B. Problems

Attempts to achieve compliance with applicable environmental health and safety standards are thwarted by a lack of adequate research and storage space. There is clearly a problem of diminishing returns if already congested laboratories are expected to absorb additional staff and equipment. This continuing problem at NIH is, to some degree, subject to controls external to NIH.

Additional staff is needed for adequate administration of programs and for fulfilling program objectives in environmental analysis, biohazard control and training.

Emergency funding from DRS allowed the Branch to fulfill required travel commitments. The problem was caused by escalating demands of extramural programs, contract management and increased staff without a corresponding increase in funds. Continuance of these trends will affect staff participation in professional affairs and training programs.

Growing concern for unsafe exposures to hazardous chemicals has revealed problems throughout the NIH environment. The total problem encompasses procurement procedures, transportation, central storage, laboratory storage, laboratory use, surplus and disposal.

Lack of adequate space for personnel and for maximum utilization of automated equipment continues to be the major problem facing the Media Unit. Loss of one-half the available cold room storage space for most of the

year, due to renovations required for solid waste handling, placed an additional burden on storage facilities. Overcrowding in areas such as media storage, bottling and plate pouring operations still exist.

C. Program Plans

Environmental analysis of the NIH programs indicates the need for additional environmental safeguards, policies and manuals. Those projects and recommendations resulting from the DHEW safety audit will receive primary Branch attention. Also, major emphasis will be placed, through necessity, on needs relative to recombinant DNA work.

Increased effort will be expended in providing training to intramural research staff in the area of biological safety. A forthcoming recommendation of the NIH Biohazards Committee will form the basis of the program. Environmental safety training for new NIH employees and student workers will also be emphasized. Educational materials being developed will facilitate this objective. B/I/D's will be encouraged to revitalize safety committees.

Recent passage of two important pieces of legislation (Toxic Substances Control Act and Resource Conservation and Recovery Act of 1976) will probably necessitate some shift of resources to respond to the requirements of the legislation. As the requirements are explicitly defined, the policy for handling and disposal of chemicals at NIH will be revised. Design modifications of existing chemical storage facilities may also be required. A complete study of NIH procedures and practices related to chemical purchasing, use and disposal will be conducted, and workload priorities will be rearranged to carry out necessary changes.

Expansion of the program to supplement in-house production of specialized media by the purchase of commercially produced routine media is planned. Increasing demands make this program mandatory in order to hasten deliveries. The need for increased automation in the plate production area to meet specialized requests has been recognized, and efforts to locate suitable equipment will be intensified.

A. Current Programs: Progress and Accomplishments

1. License Administration

During the reporting period, the U.S. Nuclear Regulatory Commission (NRC) conducted two inspections of NIH activities authorized by Licenses 19-00296-10 (broad license), 19-00296-11 (waste license), 19-00296-12 (cobalt-60 research irradiator) and 19-00296-16 (cobalt-60 teletherapy unit). Two radiation incidents previously reported to the NRC under the provisions of 10 CFR 20.405 were reviewed during the inspections. The NRC representatives were satisfied with the steps taken to minimize the possibility of recurrent incidents. The inspectors were pleased with the progress made to reauthorize radionuclide users every three years and had high praise for the quality of the NIH course, "Radiological Health for Radionuclide Users." They indicated it had a significant impact on the level of radiation safety practice of researchers and physicians working under NRC or Agreement State licenses throughout the country. They also stated that they were pleased with improvements in the NIH radiation safety program and, on numerous occasions, have referred other licensees to NIH for technical assistance, particularly in the area of controlling hazards associated with the use of I-125.

License Number 19-00296-12 was amended to increase the possession limit and source activity of a cobalt-60 research irradiator from 500 to 1,000 curies. The loading of the source into the irradiator was monitored by the health physics staff, and a comprehensive radiation survey of the facility was conducted. The results of the survey indicated a need for additional localized shielding to reduce radiation levels to an acceptable level. Additional shielding was provided, and a copy of the survey was submitted to the NRC as required by the license.

The NIH Broad Scope License (19-00296-10) was amended on July 22, 1976, to permit the use of licensed material at Danac Buildings 4 and 5. These buildings will accommodate some research activities currently conducted in the Auburn Building and at St. Elizabeth's Hospital, as well as some newly established laboratories.

License 19-00296-17 was renewed and expanded to permit installation and use of an additional 2,400-curie self-contained cesium-137 irradiator, bringing the total to three. The equipment is used to irradiate various human and animal tissues in vitro.

Special Nuclear Material License, SNM-1345, is being amended to permit surgeons of the National Heart, Lung and Blood Institute, to implant up to 25 nuclear-powered pacemakers in human beings. The newly designed units are smaller and more reliable than previous models.

The Radiation Safety Branch (RSB) reviewed 200 applications for authorization to purchase and use radioactive materials (NIH Form 465-1) and forwarded the forms to the Radiation Committee with recommendations for appropriate action; 177 received Radiation Committee approval, and the balance were rejected for reasons of inadequate training or experience.

As noted above, radionuclide authorizations now expire after three years. Reapplication and attendance at a review session is required for renewal. In conjunction with this program, 601 applications were reviewed and forwarded to the Radiation Committee for approval.

Authorized radionuclide users submitted 15 experimental protocols requesting approval to exceed NIH maximum permissible activity guidelines. They were reviewed and forwarded to the Radiation Committee with comments regarding action.

2. Radionuclide Receipt and Delivery

A total of 14,913 shipments of radioactive materials, with a combined activity of 231.5 curies, was received during the reporting period. The adjusted annual rates of increase were 17 and 23 percent, respectively. The dollar value of the materials was $2,404,632, an adjusted annual increase of 17 percent.

The Radiation Safety Branch prepared 253 packages of radioactive materials for shipment from NIH investigators to authorized recipients, domestic or foreign.

3. Radioactive Waste Disposal

Most radioactive waste pickup, processing, packaging and disposal activities were contracted on January 3, 1977, after a 20-month delay for various administrative reasons. The contract is working well, with radioactive waste generally being removed from the laboratory within 24 hours after a request for pickup. Approximately 14,000 pickups were made since the inception of the contract. The NRC was consulted and kept informed of NIH's intent to contract for this service. During the most recent inspection, it was satisfied that NIH is fulfilling its responsibilities and exercising adequate administrative controls over radioactive waste handling and disposal activities.

During the reporting period 83,632 trays of liquid scintillation vials, each containing 100 vials, were collected for packaging and burial, a 9 percent adjusted annual rate of increase over last year. The vials were packaged with an adsorbent in 55-gallon steel drums, and trucked to Barnwell, South Carolina, for burial; 2,788 drums were required. Since disposal of liquid scintillation vials by burial may be prohibited in the near future, a request has been submitted for "set-aside funds" to evaluate current and alternative methods of radioactive scintillation vial disposal at biomedical research facilities. The 55-gallon drums

were also used to dispose of compacted radioactive solid waste and solidified waste by burial; 760 drums were required.

Several computer programs were written to handle radioactive waste counting and waste inventory records. The step will enable RSB to maintain more up-to-date and accurate waste disposal records.

4. Clinical Services

Health physics support was provided to 22 patients receiving therapeutic or relatively high diagnostic levels of radioactive materials. The services included radioassay of the material administered, assistance with administration, contamination control measures, training and education of patients and personnel, personnel monitoring, and determining the patient's radioactivity level for discharge purposes. The majority of the treatments involved iodine-131 and a few, phosphorous-32 or hydrogen-3.

5. Laboratory Surveillance

There were 3,571 radiation surveys of laboratories using radioactive materials during the reporting period. Approximately two-thirds of the surveys were conducted by contract, and the remainder by RSB personnel. The latter were primarily followups on contractors' reports, or investigations of incidents or problems brought to the staff's attention by, for example, air sampling data, film badge reports, bioassays, or employees. The number of surveys performed is 40 percent below the annual rate NIH is committed to in its broad license application. This program deficiency is primarily a result of a continued 15 to 20% annual rate of increase in the use of radioactive materials at NIH coupled with increased regulatory requirements without concomitant increase in RSB staff.

Twenty-four air monitoring stations were established to continually monitor radioactivity in the effluent air from Building 10. The action was prompted by recommendation of the NRC. As a result of the increased levels of environmental surveillance and NRB requirements for monitoring workers' breathing zone concentrations of radioiodine, the number of air samples collected increased from 3,024 last year to 5,267 this reporting period, an adjusted annual increase of 39 percent.

Surveys of x-ray equipment included 120 by contract personnel and 7 by RSB staff. Also, 47 radioactive, sealed sources or foils and 181 radium-226 therapy needles totaling 575 mg were semiannually tested for leakage in accordance with Condition 17 of License Number 19-00296-10. None of the measurements indicated contamination approaching the action level of 0.005 microcuries.

6. Personnel Monitoring

Film dosimeters for evaluation of personnel exposure to external sources of radiation were processed by a commerical source. The number of NIH employees on the monthly monitoring service increased from 2,127 at the beginning of last year to 2,532 at present, a 19 percent increase. For approximately 300 persons, one or more extremity monitors are issued in addition to the body dosimeter. A total of 2 666 additions, deletions or other film badge service record changes were made by RSB personnel. Employees of the Rocky Mountain Laboratory and two Arizona field stations are also covered by this service. Additionally, radiation exposure records are maintained for approximately 200 other NIH employees working at "off-site" locations.

There were 1,346 radioassays of urine from persons working with beta-emitting radionuclides compared to 1,369 last year. The adjusted annual decrease of 21 percent was primarily due to lack of staff to evaluate and follow up on the need for bioassays and whole body counts. As a result, RSB developed an automatic data processing system to review radionuclide receipts and generate requests to investigators for a bioassay or whole body count as appropriate. However, followup on response to the requests still demands considerable staff time and is inadequate.

Whole body counts were requested for 1,415 authorized users and other laboratory personnel working with gamma-emitting radionuclides: the figure compares with 579 requests last year for an annual adjusted increase of 95 percent. The increase is due primarily to NRC recommendations for more frequent thyroid assays of radioiodine users. The evaluations are made by the Whole Body Counting Section, Nuclear Medicine Department, Clinical Center (CC); it is estimated that approximately 2,500 in vivo measurements were made at the request of this Branch.

7. Radiation Safety Training

About 1,925 man-days of training were provided to over 1,300 NIH staff members. In addition, visitors from other agencies and private laboratories attended some of the sessions. Major training sessions and attendance figures are summarized below:

Course	Number of Times Course Presented	NIH Staff in Attendance
Radiological Health for Radionuclide Users (2 weeks)	2	124
Radiation Safety Review for Authorized Users	6	111 (+4 visitors)
Radiation Safety in the Laboratory (1 day)	13	732 (+55 visitors
Radiation Safety for Nurses	18	160
Radiation Safety for Housekeeping Staff	3	150

The two-week course entitled "Radiological Health for Radionuclide Users," or equivalent training, is prerequisite to becoming an Authorized User under NIH's Broad NRC License, both for clinical and laboratory use of radionuclides. Over 300 individuals applied for the course, but only about 120 can be accommodated each year. Attendance at the one-day course, "Radiation Safety in the Laboratory," is required of employees in the radionuclide field who do not fall into the Authorized User category.

Another specialized training course given was a two-hour session for Clinical Pathology Department staff, with 25 in attendance. The one-day course, "Radiation Safety in the Laboratory" was presented to 12 members of the Rocky Mountain Laboratory of the National Institute of Allergy and Infectious Diseases and 8 visitors from the University of Montana. A Liquid Scintillation Methodology course was sponsored by RSB in January 1977, with 50 NIH employees in attendance. Two seminars on the chemical aspects of radioiodination were conducted during the fiscal year with 90 people in attendance. Branch staff also participated in a Laboratory Safety Course presented by Center for Disease Control on four occasions at various locations throughout the country.

8. Technical Assistance

The laboratories in Building 21 were used to conduct 1,280 experiments involving higher levels of radionuclides than are generally permitted by the Radiation Committee in the typical NIH research laboratory. The figure compares to 500 such experiments conducted last year, an annual adjusted increase of 105 percent.

Assistance was provided to the Phoenix Clinical Research Center in the renewal of their U.S. NRC License and in amending the license to permit the use of iodine-125 for protein labelling and in-human use. In order to justify the amendment it was necessary, among other things, to develop counting capability for thyroid assays, controls of environmental releases and procedures for monitoring airborne concentrations of iodine-125 in the laboratory.

Thirty nuclear-powered pacemakers were returned to the RSB by the National Heart, Lung and Blood Institute for transfer to the manufacturer as a result of termination of a research project. These devices had been implanted in dogs for evaluation under the provisions of License Number SNM-279. It was learned that the special nuclear material contained in the devices was the property of the Energy Research and Development Administration and, after much difficulty, the pacemakers were transferred to the Argonne National Laboratory.

Health physics assistance was provided to the Nuclear Medicine Department, CC, to improve the shielding of the xenon-127 dose fractionator, reduce personnel exposure and environmental release of iodine-131 and design a new patient treatment area.

Radiation safety inspections were conducted and training presented at Rocky Mountain Laboratory and Research Triangle Park in North Carolina. In addition technical assistance was provided to several other "off-site" locations at which NIH employees work with ionizing radiation.

RSB has assisted numerous investigators with design and fabrication of shielding, instrument calibration, optimization of counting instruments, instruction in multiple label counting techniques, instrument loans, review of experimental procedures and dose calculations.

The plans and particularly the shielding design for the Building 10, B Wing addition to the Radiation Oncology Facility were reviewed. The initial design was overly conservative, and the next submission had inadequate shielding. Plans indicating adequate and reasonable shielding were approved.

The NIH Radiation Safety Guide was revised with major changes being made relative to maximum permissible organ doses and dosimetry for internally deposited radionuclides. Information relative to 10 CFR 19 Notices, Instructions and Reports to Workers was also included. Part 19 was promulgated by the NRC subsequent to the publication of the 1972 edition of the NIH Radiation Safety Guide. Necessary clearances are being obtained and it is expected that 20,000 copies will be printed in 1978.

Technical assistance was provided to several hospitals, universities, federal agencies, commercial firms, former NIH employees and concerned citizens regarding radiation safety. Most of the private citizen inquiries were in regard to medical and dental use of x-rays. The other requests

for assistance were primarily in regard to the control of hazards from the use of radioiodine; a significant number were referred to NIH by the NRC.

B. Problems

The Radiation Safety program is caught between rising radionuclide usage, increasingly more stringent regulatory requirements and rigid personnel ceilings. The Branch has contracted for many services, increased the use of part-time personnel and overtime, re-evaluated program priorities and reorganized the program. As a result of these actions and the strong support of the Radiation Committee, significant improvement in the level of compliance with radiation safety requirements at NIH has been achieved over the past few years. However, gains made up to this time are being rapidly eroded.

A review of current services and regulatory activities indicates that it will be extremely difficult to overcome projected personnel deficits via the contract mechanism since services that can be most readily and effectively performed by commerical sources are already being handled in this manner. The RSB has arrived at a point where the time and effort spent in preparing contract specifications, evaluating contract proposals, providing adequate monitoring of the contract and maintaining administrative controls required by the NRC, exceeds the time required to conduct such activities in-house. Unless the use of radioactive materials slows or some relief is provided from current personnel ceilings, employee health and safety may be jeopardized, compliance will slip and services will deteriorate. The situation, if permitted to continue, could be a source of considerable embarrassment to NIH and result in severe curtailment in the use of radionuclides on campus, which could severely hamper the NIH intramural research effort.

The need to effectively monitor the radioactive effluents from NIH buildings has been recognized for several years. The air monitoring program for Building 21 and 10 is good. However, the exhaust air from the other buildings is sampled only twice a year by collection of grab samples, which is inadequate. In addition, routine waste water monitoring is necessary. Such sampling is difficult and complex, requiring a considerable expenditure of time and money, but air and water must be monitored in order to assure the NRC, EPA, Washington Suburban Sanitary Commission, Montgomery County officials and local residents that the radioactive waste discharged from NIH is not a health hazard.

Training is one of the key components of an effective radiation safety program. Although the level and quality of radiation safety training at NIH is considered very good, the program should be expanded. The community demand for NIH radiation safety courses, which results from word-of-mouth dissemination of scheduled training dates, cannot be satisfied. In fact, resources are not currently available to implement a radiation safety training program of the magnitude and quality necessary for NIH staff.

Another key component of an effective radiation safety program is laboratory surveillance. The level of surveillance in laboratories utilizing radioactive materials at NIH has slipped 40 percent below the level required by our license. Surveys conducted by contract are not always thorough or accurate with regard to such items as mouth pipetting, survey records, personnel monitoring and eating, drinking and smoking in the laboratories. Also, in some instances, the contractor reports contamination and none is found on a followup survey. This has required a review of the contractor's counting procedures and instrument calibration.

The Branch health physics staff has difficulty in finding time to investigate unsatisfactory conditions noted by the contractor and conduct routine laboratory surveys required by the NRC. Activities such as investigating personnel exposure to high levels of radioactive materials, responding to spills, reviewing experiments that entail considerable radiation risk, supervising radiation treatment of patients and training commitments are given priority over routine laboratory inspections and minor infractions of NRC regulations or NIH policy. The relatively large number of preventable radiation incidents occurring over the last several months is some indication that the NIH Radiation Safety program may be deteriorating from one of incident prevention to that of a crisis-centered program.

The number of individuals working off-site with radioactive materials has continued to increase in recent years, particularly within the National Cancer Institute. However, due to more immediate problems on the reservation, difficulty in identifying these individuals and their location, and limited resources, off-site radiation safety policies do not receive the attention they require.

C. Program Plans

Continued high priority will be given to Radiation Safety training as required by 10 CFR 19. Technician training will remain on a monthly basis, and attempts will again be made to develop and present an x-ray technician training program. A continuing education course for Authorized Radionuclide Users has been developed and will be presented on a routine basis. Increasing the frequency of the two-week course "Radiological Health for Radionuclide Users" to partially offset the high demand for such training cannot be attempted at the current level of staffing, and in fact, some consideration is being given to presenting the course only once a year due to the lack of personnel.

The Branch is working with the Division of Computer Research and Technology (DCRT) at the NIH in developing a comprehensive, automatic data processing system to assist in coping with the increasing flood of data handled by the Branch and in exercising administrative controls over the use of radioactive materials as required by the NRC. The Office of Management Analysis of the Division of Research Services is acting as a liaison between DCRT and RSB.

An automatic waste water sampling station will be located in the sanitary sewer system downstream from Building 21. The system will continually monitor and record the flow rate and record the total daily flow and will also be capable of collecting discrete or composite samples proportional to the rate of flow. Plans are to contract for the routine analysis of the samples.

D. Publication

Aamodt, R., Broseus, R., Swain, R. and Wagner, W.: Radiation and Radiobiology. Human Health and Disease. FASEB, 1977.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1976, through September 30, 1977

LIBRARY BRANCH Ruth C. Smith, Chief

I. SUMMARY

An Automated Circulation Control System, implemented on a limited basis for monographs in October, has increased effectiveness of services with regard to loans and processing of overdue materials. Parallel manual and automated systems were in effect until monographs and library identification cards were bar coded. The bar coding of new journal issues as received and bound volumes returned from the binder constitutes a head start toward the preparation of the journal collection for inclusion in the automated system.

A major long-term Monograph Weeding Project was initiated in May to remove old, unused and unneeded books from the Library's collection. Each monograph on the shelves is examined for retention in accordance with the Library's Scope and Coverage Policy and guidelines approved by the Library Advisory Committee. NIH investigators serving as subject consultants review decisions pertaining to retention.

Coordinated with the Weeding Project is the ongoing, but now intensified, program of selecting the latest research-level publications for addition to the collection in accordance with the Library's Scope and Coverage Policy.

Two library technicians were selected through merit promotion procedures for three-year training programs in the Technical Services Section. The programs, including on-the-job and college-level training, provide for planned progression toward positions of Technical Information Specialists GS-9 in the professional GS-1412 series.

A printer attachment to the Ohio College Library Center (OCLC) terminal provides copy of on-line data used by librarians and library technicians in cataloging new acquisitions.

The Library prepared exhibits in honor of Dr. Charles Richard Drew, father of the Blood Bank, and of Dr. D. Carleton Gajdusek, National Institute of Neurological and Communicative Disorders and Stroke, 1976 Nobel Prize corecipient in Medicine. It also presented exhibits to observe National Black History Week and National Library Week and to illustrate services provided by the Library and other Branches of the Division of Research Services.

The Training Program was designed to meet the needs of all employees with respect to their development as well as to satisfy the requirements of the Library.

II. BRANCH PROGRAMS

A. Objectives

The primary mission of the Library Branch is to operate an efficient, comprehensive Library in support of NIH scientific, medical and administrative programs. The Library selects, acquires, organizes, maintains and circulates literature pertinent to the programs and provides interlibrary loan, reference, bibliographic, translating and photocopy services. It also develops, maintains and services a collection of material in nonprint media pertinent to the scope of the Library and provides equipment for its use. The staff verifies citations, compiles short reference lists and makes literature searches upon request. Bibliographic assistance is provided through medical, chemical and biological computer searches of the National Library of Medicine's MEDLINE, Chemical Abstract's Chemical and Biological Activities (CBAC) and Biological Abstract's BioSciences Information Service (BIOSIS). Library Services Advisers integrate resources and services available in and outside the NIH Library, such as specialized information centers, computerized information retrieval systems and clearinghouses.

B. Program Progress and Accomplishments

Technical Services

Operations of procurement, organization and processing of monographs, journals and other forms of literature functioned at slightly above the FY 76 level. Several large projects were accomplished with the assistance of employees from other areas of the Library and summer students and by use of overtime.

A major bar-coding identification project for labeling each monograph in the Library's collection as required for the Automated Circulation Control System was completed within five months. Bar coding was instituted for new journal issues as received by the Library and for bound volumes returned from the binder. Earlier journal volumes in the collection remain to be labeled.

A substantial long-range undertaking is the removal of all catalog cards and other Library records representing each monograph identified as not needed in the Library by the Weeding Project.

A printer attachment to the Ohio College Library Center (OCLC) terminal has eliminated the need for manual notes by librarians and library technicians. Provision of hard copy has made use of the cataloging data base increasingly efficient and effective.

Acquisition of small desks and chairs and individual bookshelves has increased the working space for employees and permits a less cluttered arrangement.

Readers Services

Operations of library copy services and shelving and stacks maintenance increased considerably over FY 76 levels. Interlibrary loan and nonprint media rose slightly and circulation remained relatively stable.

Extensive shifting of the main journal collection on the lower level was again necessary this year to relieve crowded stack conditions and to include journals published in 1971 from the Last Five Years collection on the upper level.

The Automated Circulation Control System was put into operation for monographs on a limited basis on October 18. Parallel manual and automated systems were in effect for charges until all monographs and library identification cards received bar-coded identification labels. This period was longer than anticipated due to lengthy delay in filling the order for plastic cards used for identification cards. Computer-generated overdue notices were mailed out beginning in April; the use of "Materials on Loan" on microfiche increasingly replaced the monograph charge file as manual charges decreased. Training employees in operating the minicomputer system was aided by the use of two guides, Users Manual for the NIH Circulation Control Computer System and the NIH Library Circulation System/IBM 370 System Documentation, prepared by James M. Deleo and Dennis George, respectively, both in the Division of Computer Research and Technology.

A new copy machine was installed after a test period to replace the worn-out machine used by the Library staff. This machine also serves as backup equipment when the self-service machines break down or are under unusually heavy demand.

The Catalog of Audiovisual Materials prepared by the Nonprint Librarian was printed and distributed to NIH staff who receive the Librarian's monthly Memorandum.

Reference and Bibliographic Services

Requests for reference services and for MEDLINE and other computerized bibliographic services increased over FY 76 levels. Some 13,270 reference questions were received at the reference assistance desks and over the telephone. MEDLINE searches amounted to 13,920, an increase of 27.4% over last year. Approximately 5,000 computer-generated bibliographies were provided investigators who are entered on the current awareness list.

A long-term Monograph Weeding Project was initiated in May as the first major weeding of the collection since 1970-72. Each monograph on the shelves is examined to determine whether it should be retained in the Library's collection in accordance with the Scope and Coverage Policy of the NIH Library and guidelines approved by the Library Advisory Committee. Monographs being considered for withdrawal are placed on designated shelves for a month for review and recommendations by NIH investigators serving as subject consultants. Recommendations concerning these books are also received from other interested NIH staff members.

An energetic monograph selections program has been coordinated with the Weeding Project. Selectors are intensifying the ongoing program of developing and supplementing the Library's collection by locating the latest research-level literature which is pertinent to the needs of the NIH community.

Translating Service

Approximately 1,200 requests were received for translating services, which represents a decrease of 17.2% from FY 76. Of the total requests received, 350 were for oral translations, 50 for recorded translations and 550 for written translations; existing translations were located for 250 requests. Contractual firms made 350 written translations and Library translators 200, with total words amounting to over 2 million. All contractual translations were reviewed for quality in the Library.

Training

The FY 76 Training Program provided employee training in academic, professional, governmental, administrative and technical courses selected to meet individual needs for development and improved performance on the job. Forty-seven employees received 3,900 hours of training in 130 courses. Ten employees participated in Adult Education and Upward Mobility College training. Two library technicians in three-year trainee programs in the Technical Services Section received a total of 588 hours of training in 18 courses, as well as on-the-job training. Several other on-the-job training courses were provided employees within the Sections.

Exhibits

Exhibits prepared by Library staff include displays in honor of Dr. Charles Richard Drew, father of the Blood Bank, and Dr. D. Carleton Gajdusek, NINCDS, 1976 Co-winner of the Nobel Prize in Medicine. Other exhibits were presented to observe National Black History Week and National Library Week, to illustrate the activities of the Division of Research Services' Veterinary Resources Branch and Environmental Services Branch and to outline computerized bibliographic services provided by the NIH Library. Art assistance for the exhibits was given by the Medical Arts and Photography Branch.

C. Problems

Limited space in several areas of the Library will be a major problem in the very near future. Plans are being formulated now to alleviate problems in some areas before crisis situations occur.

At the end of the calendar year, the shift to the lower level of 1972 publications from the Last Five Years collection will provide some space on the upper level, but much of this will be used for new titles. Also, space available on the lower level will become severely limited. Steps taken to reduce the number of second subscriptions to some journals and to purchase other titles in microform will help. Expansion to selected areas on the third level of the Library building will provide much needed storage space for older titles

which are to be retained in the collection. The process of reducing older titles to one of the microform formats is being investigated.

Space is also acute in the Abstracts and Indexes area on the upper level. Several titles have been shifted to the lower level, an inconvenience to some users.

Library users and members of the Library Advisory Committee have suggested that a reading room be established to provide better control of new journal issues, which often cannot be located on the shelves designated for them. No space is readily available; the room should be on the upper level near the reference assistance desk. Provision of an enclosed area is being investigated.

Additional work space is still needed for the Technical Services Section. With the release of requested space on the third level of the Library building, the bindery operation will be moved there and at least several members of the Section will be relocated in the vacated space.

D. Program Plans

Plans will be developed to study the feasibility and potential benefits of making the Library's holdings accessible via remote terminals located in the Institutes and Divisions. The end result of such an undertaking would be an on-line catalog, readily available near the work site, which would provide faster document delivery. The MESH (MEdical Subject Headings) Project, for conversion to specialized National Library of Medicine headings for medical books, will be incorporated into the plan.

The Library also intends to develop an automated In-Process File for monographs, using the Library's minicomputer. The file will contain a bibliographic description of each newly acquired item and status information as it progresses through the processing stages. All records will be transient, expendable once the item is processed for payment, fully cataloged, announced in the list of new acquisitions in the Librarian's monthly Memorandum and added to the master file of Library holdings.

The Monograph Weeding Project will continue with the assistance of NIH researchers and scientists. An aggressive book selection program will be pursued to upgrade the collection.

Access to additional automated subject data bases will be investigated through the Federal Library Committee.

A study of the photocopy process to determine the feasibility of replacing the present system with another method, such as microfiche printing, will continue.

E. Publications

National Institutes of Health Library: Memorandum: Recent Additions to the NIH Library. Monthly (Internal Use Only).

Stroman, R. H.: Government Libraries. In Josey, E. J. (Ed.): Opportunities for Minorities in Librarianship. Metuchen, N. J., Scarecrow Press, 1977, pp. 167-177.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1976, through September 30, 1977

MEDICAL ARTS AND PHOTOGRAPHY BRANCH Mr. Arthur F. Moore, Chief

I. SUMMARY

Requests for MAPB services increased approximately 10 percent in FY 1977. The heavier workload was met by a corresponding increase in contract services. Delivery of finished artwork accelerated during the year. The time needed for normal photographic service remains at five work days, but some emergency requirements are handled in 24 hours. The graphics standards established for statistical materials produced by the Branch continue to broaden in application toward a unified visual communications system for the NIH. With new equipment, wider use of contract services and training, the Branch intends to expand its skills and meet rising demands for services.

II. BRANCH PROGRAMS

A. Objectives

The objectives of the Branch are to provide consultation and production services to the NIH; to visually communicate program efforts and research results; to provide skills and techniques in visual design, medical art, applied arts, still photography and cinematography for solving problems of recording, communicating and presenting research activity; and to investigate, develop and upgrade visual techniques.

In meeting NIH research program demands, the Branch supplies professional services competitive with commercially obtainable services at the lowest possible cost. It develops specialized capabilities, particularly in graphic presentation, still photography, cinematography and medical arts tailored to NIH needs.

The Branch monitors art and photography services procured by outside contract, serving as a technical adviser in obtaining needed additional services at the lowest cost consistent with high quality.

B. Current Programs

Programs of the Branch are still and motion picture photography, including photomacrography, photomicrography, cine photomicrography, high-speed cinematography, general photography and related laboratory services; visual arts production including publications design and general graphics; visual aids including slides, vu-graphs and other projectables; animation artwork; technical, general and medical illustrations; exhibit design; statistical drafting; display charts; and medical models.

C. Program Progress and Accomplishments

Increased demands for services were made of the MAPB this year, climaxed by the intense activity created by the Federation of American Societies for Experimental Biology Meetings.

The graphic design manual prepared by the Branch to upgrade visual communications is being widely accepted. The manual achieves uniformity of graphics quality, improves communications and effects savings by establishing standards and eliminating preliminary design problems.

The Photography Section instituted technological improvements in the areas of photomicrography, photomacrography and photographic laboratory services. The improvements were accomplished by formal technical training and attendance at seminars and professional meetings as well as by replacing old equipment with advanced photographic tools. Firm and fair leadership, imaginative management techniques, communication between first line supervisors and employees and appropriate training have enhanced employee morale and the quality of photography production in the Section.

The Photography Section extensively utilized outside vendor services from private photo firms in the D.C. area, in addition to in-house facilities, in order to keep pace with the ever increasing calls for photography services by the National Institutes of Health.

The Design Graphics Section possesses a nucleus of well-trained, extremely dedicated personnel. This group enables the section to respond to extraordinary requests for complex visual productions, which are continually mounting in numbers. The Section had a productive year, augmenting output 10 percent, with no increase in personnel and maintaining its usual high quality production. The Section has a spirit of pride in its ability to expeditiously handle any visual production requirement of the biomedical community.

Requests for medical illustrations remained at a normal level throughout the year. Contracting was seldom used since few projects entailed short deadlines. Calls for medical models remained about the same as in FY 1976.

The Motion Picture Section, in addition to filming an average of 3,900 feet per month, made seven formal productions, an increase of 75 percent.

MAPB personnel spent 1,013 hours in formal training courses at a cost of $4,157.00.

The Branch's negotiated agreement with AFGE Local 2419 was automatically renewed for another two-year period. Relations have been smooth and without incident.

A thorough ongoing program to familiarize Branch employees with Equal Employment Opportunity goals and all aspects of the merit promotion plan continued.

D. Problems

In many instances, the NIH community still does not allow sufficient lead time for planning and execution of audiovisual materials. Needless demands for rush work deprive other NIH staff members of services they deserve. The Branch has extensive expertise in planning and conversion of raw data into effective multimedia presentations. The counsel is readily available in all areas of MAPB, or on location, and should be used earlier and with more frequency.

Even though an extensive study revealed that the proposed Graphics Unit of the Design Graphics Section should most appropriately be supported through the Services and Supply Fund, the Division of Financial Management would not approve conversion from the Management Fund at this time. The denial is regrettable because it prevents faster delivery and a more effective use of manpower at the MAPB.

E. Program Plans

The Medical Arts & Photography Branch will pursue the development and implementation of a system to upgrade NIH visual communications. It will aim to improve, enlarge and extend its services and will seek additional ways to acquaint the NIH community with its skills. The importance of early counsel and planning, for optimum service, will be emphasized.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1976 through September 30, 1977

Veterinary Resources Branch Dr. Robert A. Whitney, Jr., Chief

I. SUMMARY

The Veterinary Resources Branch (VRB) provides NIH investigators with living animal models and biological products for medical research. The Branch also supplies facilities and services related to the use of the models and functions and performs collaborative research.

Animal production is limited to animals that are not available commercially or cannot be procured with quantity and quality guaranteed. In addition to the 515,000 rodents and rabbits, small numbers of purebred foxhounds, rhesus monkeys, goats, burros, and miniature swine were produced by the Branch in 1977.

Production of biologics included blood or serum from a number of species of ungulates and 3,600 units of canine blood from the universal donor foxhound colony.

Procurement of rodents and rabbits increased considerably from 150,000 last year to 235,000 in 1977. Utilization of dogs by NIH investigators continues to decline; only 360 foxhounds were procured in 1977 versus over 700 in 1976.

Nonhuman primates, cats, ungulates, and feral animals were purchased and conditioned. Although not well defined genetically or microbiologically and of lower quality than NIH-bred animals, they are satisfactory for certain studies. The animals are quarantined before being used in research programs and, during the quarantine period, given appropriate immunizations, tested for a variety of infectious agents, and treated medically as required.

Services and collaborative support to NIH investigators increased significantly in several areas such as gnotobiotics, animal holding, and genetic monitoring of inbred strains of rodents. Major research contributions were made in the development of a number of new animal models for human diseases. Additional "markers" to aid in establishing genetic profiles of inbred mice were developed and efforts were continued to prevent or control a number of diseases in laboratory animals that interfere with their use as research tools. Nutrition research permitted development of open formula rations for all of our rodent colonies, improving reproduction performance and decreasing cost.

In addition to supplying animals for intramural investigators, breeding nuclei from our WHO genetic resource were provided to the international biomedical research community since many stocks, strains, and substrains are not available elsewhere. About 240 investigators at 200 institutions were provided 5,565 animals to start breeding colonies.

All major small animal contract programs at the National Cancer Institute (NCI) are now relying on VRB as the genetic base for their colonies. Germfree and pathogen-free animals were provided as pedigreed breeding nuclei for the Frederick Cancer Research Center (FCRC) and other Division of Cancer Treatment and Division of Cancer Cause and Prevention contractors.

II. BRANCH PROGRAMS

A. Current Programs: Progress and Accomplishments

1. Animal Center Section

Goats and blood group CEA 1, 2, and 3 negative foxhounds are produced in breeding herds and colonies at the NIH Animal Center in Poolesville, Maryland. Foxhounds, rhesus, and squirrel monkeys are bred and raised by contractors. Nonhuman primates, cats, ungulates, and feral animals are purchased and conditioned.

This year the conventional foxhound breeding colony was increased 40 percent, to 176 bitches and 25 stud dogs. Culling continues to be directed towards eliminating poor producers, genetic disorders, and chronic disease problems. The inbred foxhound colony consists of one English and two American (Walker) foxhound lines. All lines have reached the third generation of inbreeding. Development of these lines is being directed principally towards providing a genetically uniform research dog for NIH investigators.

Serum from all foxhound production bitches is being analyzed for fetal antigens. Histocompatibility typing is being conducted on donor dogs and inbred lines, and further red blood cell typing is being done on the donor dogs in cooperation with Michigan State University.

Approximately 240 purebred foxhounds were supplied by a contractor. As purebred stock at NIHAC increased and issues decreased, 510 fewer contract-produced dogs were required this year than in FY 1976.

Only 120 foxhounds of random source were purchased this year, compared to 360 in FY 1976. Requests for random-source cats appear to be stable; projected issues remain at approximately 800.

The goat breeding herd was expanded from 30 to 50 does and 2 bucks; 49 kids were born to 25 does. Goats produced from the breeding herd will be held until approximately 1 year of age before issue.

The number of inbred miniature swine maintained and bred for NCI has increased to about 100. A temporary swine building was purchased and constructed on the leased property to house approximately 125 animals.

Approximately 700 ungulates will be purchased, quarantined, conditioned, and issued this year. Some 180 domestic fowl, including ducks, chickens, and turkeys will be utilized, which represents an increase of 100 percent over FY 1976.

Rhesus (Macaca mulatta) monkey issues are estimated at less than 2,000, a substantial decrease over last year. The decline is due primarily to decreased polio vaccine testing by the Bureau of Biologics, FDA. There were 120 rhesus monkeys purchased, quarantined, selected, and delivered to the facility at Perrine, Florida, for replacement breeder stock. Requests for cynomolgus monkeys have been very low, despite efforts to advertise their availability. Only 33 animals were issued.

Other species of monkeys (Erythrocebus patas, Saimiri sciureus, Cercopithecus aethiops, Aotus trivirgatus, and Saguinus sp.) contributed small numbers to the quarantine and conditioning program. With the consent of investigators involved, small groups of owl monkeys (four pairs) and marmosets (one pair) were kept as breeders. From these, three owl monkey births and two marmoset births have resulted.

A New World primate breeding project to establish animal models for reproductive physiology has been initiated. This program is in the architectural design stage with several facility designs being considered. Building 103 "300" corridor is being utilized in the interim.

Primate health records are being computerized. The data, including monthly reports and epidemiologic survey information, will soon be available to investigators.

Additional space was made available to house research dogs on a long-term basis. Approximately 160 experimental dogs are maintained on a continuing basis, which is twice the number held in FY 1976. Holding livestock produced by breeding herds for investigative purposes during quarantine and transit between contract and laboratory facilities increased from 750 in FY 1976 to 900 this year.

Holding of Peruvian marmosets and squirrel monkeys from the NIH-Pan American Health Organization contract was initiated this year. A small harem breeding group of squirrel monkeys was maintained for the National Institute of Allergy and Infectious Diseases. Several females in this group have become pregnant.

Renovation of the sheep barn on the leased property was completed and will allow expansion of sheep holding to 200.

In addition to producing and holding animals, the Animal Center Section produces biologics. Domestic turkeys, chickens, and ducks were utilized at a greater rate this fiscal year to produce normal blood and antisera for specific research projects.

The 234 dogs in the canine blood donor colony produced an estimated 3,600 units of blood (1 unit = 500 ml). Inbred stud dogs from the breeding colony are also now utilized as blood donors when demand is high, which allows some reduction in the number of kennels needed to house donors and makes more space available for long-term holding.

Biologics production from ungulates was slightly more than last year. Projected production is 1,400 liters of ungulate blood for the year.

Animal Center surgery facilities were utilized for porcine transplantation studies and to treat a variety of diseases in laboratory animals.

Radiographic procedures remained at approximately 450 exposures. Installation of an automatic processor increased the capabilities and efficiency of radiographic procedures.

Fecal culturing for Mycobacterium paratuberculosis (Johne's disease) in the goat herd continued. There were 11 cases of the disease this year. Selected kids have been reared from birth away from other goats in an attempt to establish the nucleus for a Johne's-free herd. Brucellosis testing is performed annually in the canine breeding colony, swine and goat herds, and sheep flock. No new cases were observed.

2. Comparative Pathology Section

The staff of this section provides diagnostic services, laboratory assistance, training, and administrative liaison for investigators concerned with disease control in animal colonies in NIH intramural laboratories. Disease problems are dealt with in conventional, germfree, and barrier-maintained colonies. Monitoring for a wide variety of microbiologic agents and parasites is performed routinely. Tissue processing services are also provided. Research on the pathogenesis of diseases occurring naturally in laboratory animals is conducted to facilitate diagnosis and control.

The Animal Disease Investigation Service answered 341 calls this year, slightly fewer than the previous year. The calls for consultative, diagnostic, and therapeutic services were received from all Institutes. Animal species involved included rodents, rabbits, primates, carnivores, and feral animals. Supplemental pathology exams were required in 147 investigations, microbiologic testing in 57, and clinical pathology tests in 26. This service continues to be well received by NIH scientists and mutually beneficial to the investigators and the VRB staff.

Studies of the natural history of Tyzzer's disease using the complement-fixation test showed that the infection was prevalent in wild cottontail rabbits. Seronegative cottontails held in captivity for several years are extremely susceptible to infection. The findings suggest the likelihood of contamination of food for laboratory animals by excrement of wild rabbits containing the spores of Bacillus piliformis, as well as the probability of Tyzzer's disease being one of the major causes of periodic die-offs of rabbits in the wild.

Officials at the Center for Disease Control (CDC) in Atlanta requested isolates of the causative agent of Tyzzer's disease (of both rabbit and horse origin) for study of the respiratory illness in man known as Legionnaire's disease. Although the Tyzzer's agent (horse origin) could not be linked to Legionnaire's disease, it was shown that sera from each of several patients who recovered from Legionnaire's disease had significant levels of antibody to Tyzzer's agent (titers of 32 to > 512 using the fluorescent antibody technique). Such a finding suggests the need for further investigation of the possibility that the Tyzzer's agent infects man. The Comparative Pathology Section has used the complement-fixation technique to examine the sera of persons who have worked with the Tyzzer's agent in our laboratory and of persons who have contact infected animals for several years in the Small Animal Section of our Branch and have not found antibody to either isolants of the agent causing Tyzzer's disease. Such sera should be studied using fluorescent antibody technique.

CDC also requested assistance in the investigation of an epizootic of hemorrhagic disease in the facilities of a commercial monkey supplier in New Jersey. Pathology studies revealed lesions that were typical of Simian Hemorrhagic Fever (SHF), a viral disease of Macaca sp. which was first described at NIH in 1968. The commercial supplier was holding 70 patas monkeys suspected of being subclinical carriers of the disease and the source of infection for the macaques. In an effort to prove that the patas were carrying the virus, samples of their serum were combined in four pools and a 0.5 ml sample from each pool was injected into a M. fascicularis. The injected monkeys died five to six days after inoculation and had typical lesions of SHF.

The Comparative Pathology Section monitors the genetic integrity of inbred mice by testing for groups (profiles) of characteristics (markers) which identify the genetic constitutions of each strain. The profiles consist of morphological, immunological, and biochemical markers of 31 loci on 15 of the 19 mouse autosomes. The profiles also are used in investigations of suspected genetic contamination in animals in NIH laboratories. Research is aimed at refining and developing new marker systems and establishing profiles for monitoring additional genera of animals used in biomedical research.

At the request of officials of the International Committee on Laboratory Animals, the genetics program accepted responsibility for supplying genetic profiles for monitoring the 20 strains of mice congenic with the nude (athymic) gene. International scientists will compare profiles of their nude inbred strains with those of the NIH reference strains.

A collaborative program between a laboratory at Sloan Kettering Cancer Center and the genetics program was established. Staff at Sloan Kettering agreed to type the lymphocyte surface antigens, LY-1, LY-2, LY-3, and THY-3 in the inbred strains of mice maintained by VRB. In return, the genetics program will type the inbred strains maintained in the Sloan Kettering laboratory for several biochemical markers.

Two C57BL/6N female mice, bred in the Small Animal Section expansion colony, produced both black and brown progeny when mated to BALB/c males. Assessment of seven genetic markers on five chromosomes demonstrated that two of the markers are on the same chromosome as the black-brown coat color gene. The data indicate that the occurrence of the brown progeny was the result of a point mutation at the coat color locus from black to brown and not due to gross contamination of the C57BL/6 colony. Examination of pedigreed C57BL/6 mice showed that the mutation could not have occurred in the foundation colony but rather in the expansion colony.

A genetic contamination of (CBA x BALB/c) F_1 hybrid mice was discovered. Investigations of isozyme characterization disclosed that a F_1 hybrid female (phenotypically identical to the CBA female parent) was left in the breeding cage and produced offspring by her BALB/c father.

One of the Institutes requested that the genetics program determine the inbred strain of origin and possible contamination of two tumor cell culture lines, a spontaneous thymoma and a carcinoma of unknown tissue origin. The thymoma is known to have come from an AKR/J mouse and the carcinoma is thought to

have come from the same strain. The two tumors exhibited atypical growth patterns when introduced into AKR/J mice. Since tumor cell lines from both AKR and A strains were being maintained in their laboratory, the possibility of cross contamination existed. The enzymes malate dehydrogenase (Mod-1) and isocitrate dehydrogenase (Id-1) were used as genetic markers to differentiate between strains AKR/J and A/J. The results of the studies indicate that the strain of origin for the carcinoma was not AKR/J but probably the AKR/Cum subline. The conclusion is consistent with the atypical growth pattern observed when the tumors were inoculated into AKR/J mice.

3. Small Animal Section

This section issues small research animals, which include valued genetic strains, to intramural investigators, contractors, and national and international biomedical communities. It also maintains animals during gnotobiotic experimentation and provides collaborative research support. The professional staff does research and furnishes advice on animal health, nutrition, care, and husbandry and develops animal models for human diseases.

About 515,000 VRB-produced rodents and rabbits were issued to investigators, slightly more than the number produced last year. Requirements for and production of VRB inbred and noninbred mice, noninbred rats, and hamsters increased. All demands for VRB strains and stocks of mice were satisfied. Approximate animal issues were as follows:

Inbred mice	275,309
Noninbred mice	182,578
Inbred rats	10,269
Noninbred rats	22,048
Inbred guinea pigs	11,622
Noninbred guinea pigs	5,668
Hamsters	6,382
Rabbits	1,051
Germfree rats	534
Germfree mice	279

The Frederick Cancer Research Center continued to rely on VRB foundation colonies as the genetic base for their rodent colonies. Pedigree mouse and rat strains were supplied from both the VRB barrier-maintained and germfree colonies. VRB has also assumed the responsibility of maintaining the genetic base for a variety of other NCI contract programs requiring germfree pedigreed stock and breeding nuclei of mice. This is the second year the Division of Cancer Treatment has utilized this service.

In addition to supplying animals for intramural investigators, breeding nuclei from our WHO genetic resource are provided to the biomedical research community since many of the stocks, strains, and substrains are not available elsewhere. About 240 investigators at 200 institutions were provided 5.565 inbred and noninbred animals to start breeding colonies. This includes 2,780 mice, 1,410 rats. 1,330 guinea pigs, 25 hamsters, and 20 rabbits. Several commercial producers were also provided with breeding stock.

investigators' needs are the dwarf, beige (Chediak-Higashi syndrome), and motheaten (hypergammaglobulinema/hyperautoimmunity) genes.

Animal model development utilizing the rat colonies is also progressing satisfactorily. The corpulent gene is being introduced into hyper and normotensive strains to permit studies on the relationship of corpulence to blood pressure. Similarly, the diabetes insipidus gene is being introduced into normo and hypertensive strains.

Efforts continue to develop acceptable pathogen-free rabbits. Although VRB strains are free of the common rabbit pathogens, including Bordetella, Pasteurella, and Eimeria, mortality from cecitis is excessive. Attempts also continue to develop pathogen-free guinea pig colonies in the barrier and in F-wing. Reproduction of barrier-maintained animals is poor, while that of guinea pigs in F-wing has been satisfactory.

The number of germfree isolators available for research use by NIH investigators was increased from three to seven.

The long-term goal of developing open formula diets for all rodents and rabbits maintained in the Small Animal Section was achieved in 1977. The major advantages of using such diets are increased reproductive performance, decreased feed costs, and greater assurance of quality. Increasing numbers of institutions throughout the biomedical research community are now using the NIH open formula diets (known amount and types of components) for both experimental and production colonies of rodents and rabbits. Experiments were proposed to evaluate the diets under conditions of commercial production for three NIH animal suppliers. One of the open formula diets has been recommended as the national ingredient standard reference diet for research by the American Institute of Nutrition. No major problems occurred with any of the animal feeds. Assays indicated that all feeds purchased under contract were in compliance with the specifications.

A series of special diets was formulated to study the effect of various dietary fats on the development of atherosclerosis in swine and dogs, the influence of sources of dietary fiber on carcinogenesis in rats, and the effects of varying concentrations of fat and protein on carcinogenesis in mice. Adjustments were made in several existing open formula rations to accommodate the special requirements of specific NIH research projects. Purchase specifications were prepared to provide special diets for eight investigators. A diet was formulated using ingredients with low contamination potential to accommodate toxicologic studies.

Studies were initiated to develop purified diets and establish nutrient requirements for laboratory animals. A purified diet for mice prepared in collaboration with the American Institute of Nutrition is now widely used in the research community.

4. Veterinary Medicine and Surgery Section

This section provides complete facilities for experimental surgery on research animals. The facilities are available to all NIH investigators and include

equipment for anesthesia, physiological monitoring, and radiographic studies; a 500-milliampere radiographic unit with fluoroscopy is available. Services are furnished to assure humane and aseptic technique. Upon request, staff veterinarians will perform surgery, collaborate in the preparation of animal models, and provide advice on research protocols. Complete veterinary service including pre and postoperative medical care is provided, to assure optimum health of all NIH animals. Approximately 650 surgical procedures were carried out, despite the inconveniences of renovation. The new location of the surgical facility in Building 14E permits more space for an increased number of procedures.

Experimental surgery performed this year was often complex and included numerous thoracic, cardiovascular, fetal, neurosurgery, and abdominal procedures that demand a high level of technical support. Operations were done on dogs, cats, guinea pigs, hamsters, chickens, monkeys, rabbits, and larger animals.

The Primate Research Unit started a primate reuse program to facilitate exchange of primates among NIH intramural investigators when programs are completed. The unit receives primates from investigators, provides credit to the investigators' common accounting number, and reconditions the primates before reissuing them. The program promotes conservation of primates and decreases the demand for new animals. Complete medical and research records are maintained for each animal in a computer bank storage file. Ready access to this information for NIH investigators eases the exchange and reuse of primates among intramural investigators.

In-house and contract breeding colonies meet the needs of NIH scientists. The Primate Research Unit of VRB maintains a breeding colony of rhesus monkeys and baboons to provide timed pregnant females and neonates; 69 timed pregnant rhesus monkeys and 35 timed pregnant baboons were issued during the year.

The in-house timed pregnant rhesus breeding colony currently consists of 53 breeding females and 28 breeding males. During the year, 20 nonproductive females from the in-house colony and 60 from the contract breeding program were reassigned to the newly established primate reuse program. Of the 60, 20 will be added to our colony, and 40 will be sent to the contractor. Semen studies are being made of breeders to identify nonproductive males, which will be made available for reuse.

The holding capacity for research primates increased from approximately 650 in FY 1976 to 1,800 in FY 1977, after completion of renovations in Building 14D, a joint venture between DRS and FDA. Utilization of holding space will probably exceed 90 percent by September.

The research holding facilities of Building 28 has increased its scope of research support by greater diversity of animal species including dogs, cats, miniature swine, goats, sheep, and other large laboratory animals. In addition, new collaborative DRS research programs with NCI and the National Heart, Lung, and Blood Institute (NHLBI) have been implemented. Atherogenic diet research on dogs and miniature swine led to development of an integrated research facility suitable for complex experimental protocols using larger laboratory animals.

The population of research animals in this facility averages approximately 380 per month. Research animals requiring infrequent investigator manipulation are maintained on contract, also, which facilitates management by permitting a more suitable animal density population per kennel. Renovations of the indoor-outdoor research animal holding facilities are scheduled for implementation during this fiscal year.

B. Problems

1. Animal Center Section

Stray dogs were a nuisance on several occasions. In June, 11 goats were killed as a result of dogs attacking the herd.

The availability of quality blood group CEA 1, 2, and 3 negative, microfilaria-negative, dysplasia-free dogs for the breeding colony continues to be limited, but 46 bitches have been retained, increasing productive females by 39 percent. Many bitches are becoming aged, which compounds the problem of attaining a maximally productive colony. Some male dogs have been obtained from outside sources to reduce the coefficient of inbreeding.

NIH utilization of dogs this year was the lowest of any year on record. Issues declined by 23 percent compared to last year. Lower procurement of contract dogs will allow more kennel space for growing colony-produced dogs and long-term holding.

Decreased monkey issues caused financial problems early in the year. The price structure was established on the basis of an anticipated 3,300 issues. However, the Bureau of Biologics, (BoB), used only about 1,100 of the 2,300 forecast. To help alleviate the problem, the Primate Quarantine Unit (PQU) preissued 500 monkeys to BoB and maintained them for a per diem rate.

Monkey breeding contractors are expected to produce 970 progeny per year by 1980. The NIH estimated requirement for small rhesus monkeys in FY 1978, excluding BoB, is only 200. The estimated large rhesus monkey requirement for FY 1978 is 550. Since BoB is trying to become self-sufficient, with their own breeding colonies, VRB will be producing approximately 570 too many rhesus progeny annually unless the PQU holds them long enough to supply the requirements for large monkeys or issues are made to other government agencies. The problem is being evaluated for its future impact on supply and economics. Excess progeny will continue to be supplied to BoB until their colonies are fully developed, which may be in FY 1979.

The incidence of tuberculosis among imported rhesus monkeys was 2 to 3 percent. One entire shipment containing several anergic animals had to be destroyed after 8 months of testing produced a number of reactors. Mycobacterium bovis, a slow, invading, tubercular organism, was incriminated in the outbreak.

A shipment of marmosets was decimated by pneumonia soon after their arrival. They arrived in anorexic dehydrated state, heavily parasitized by Prosthenorchus sp. and several kinds of microfilaria. The animals died rapidly with extensive pneumonic lesions and nephrosis. Klebsiella pneumoniae was isolated in pure culture from the lungs.

Limited monitoring of animals by contract for NIH was begun. Animals to be tested were purchased as part of routine orders to avoid bias by the suppliers in selection of the animals. Because of manpower shortages and the need for practicality, the samples of animals are small and proportional to the estimated sizes of colonies from which they are derived. Also, no effort is made to regulate the location of sampling in rooms or buildings. The monitoring is limited to tests for Salmonella sp., ecto and endoparasites, and certain murine viruses appropriate for the different strains of animals. The viral testing (serologic) is performed by a commercial contractor. To date, the results indicate that the rodents from all the suppliers have antibody to one or more viruses that cause disease problems and interfere with research in NIH laboratories. For example, antibody to Sendai virus or pneumonia virus of mice or both have been found in all five of the major suppliers tested so far. Heavy mite infestations were found in one supplier's animals and pinworms were found in another.

Some serious infections in NIH rodents were uncovered by the Animal Disease Investigation Service. Examples include several outbreaks of mycoplasma pneumonia in mice, streptococcal pneumonia in rats, and chronic respiratory disease in rats. The incidence of such diseases in NIH animal rooms is relatively high because the rooms are not designed to house several species of animals derived from multiple sources.

Two outbreaks of fatal coccidiosis in young guinea pigs occurred in an animal colony in the BoB. The gametocyte stages of Eimeria cavae were present in tremendous numbers in the colon mucosa, indicating that the animals were heavily exposed to oocysts approximately nine to ten days before death, while they were still on the premises of the animal supplier. Investigations revealed that the supplier had well-maintained, coccidiosis-free colonies for production of guinea pigs for NIH, but also produced some guinea pigs at another location in large floor pens in which the bedding was seldom changed; that environment would promote development of a number of diseases and, especially, coccidiosis. Animals from the floor pens were probably sent sporadically to NIH when large orders could not be filled.

3. Small Animal Section

Cecitis in C-wing rabbits continued to be a major problem, resulting in 366 deaths (457 projected to a 15-month period). The cause is still unknown, although previous studies suggest that the disease may be due to imbalances of intestinal microflora and may be exacerbated by antibiotics. One severe outbreak resulted in 85 deaths in a month. As in a previous year, the outbreak followed antibiotic therapy for Tyzzer's disease. Tylosin appeared to be implicated more than tetracycline.

Since a rotavirus was reported in rabbits with diarrhea in England last year, an effort was made to demonstrate such an agent in the rabbits with cecitis. In collaboration with NIAID investigators, fecal filtrates from 20 rabbits were clarified and examined for viral particles by electron and immunoelectron microscopy. No viral particles were found.

The disparity in pay between biological laboratory technicians working in the barrier and animal caretakers working in conventional colonies is not resolved. The situation, where technically skilled workers are paid less than those performing less complex work, results in recruitment difficulties and poor morale. It will be very difficult to effect program changes involving increased emphasis on highly technical programs if the problem continues.

4. Veterinary Medicine and Surgery Section

Phase I of Building 14E will be completed soon, which will allow the surgery unit to move into the newly renovated area and initiation of Phase II renovations. The lack of a functioning air conditioning system and overhead surgery lights will pose some problems with aseptic techniques. Until renovations are accomplished, the surgery unit is functioning with a variety of inconveniences that require investigator and employee tolerance.

It is hoped that funds will be available during FY 1978 to accomplish renovation of the heating and cooling system in the old wing of Building 14D. The system is well below minimum standards established by DHEW guidelines. Renovation will disrupt primate holding rooms and require transfer of primates within Building 14D. The possibility exists that it may be necessary to limit acceptance of new research primates due to loss of this space during renovation.

C. Program Plans

1. Animal Center Section

The canine socialization program for colony-reared dogs, which was formally initiated in FY 1976, is continually being refined to increase their quality and the efficiency of the program. In the future, more input from investigators using the dogs will be sought to better evaluate the program.

Contract production of purebred foxhound puppies (over 500 in FY 1976) was reduced to 240 in FY 1977. Increased NIHAC dog production with the development of additional outdoor housing space is expected to replace the need for all contract-produced dogs by mid-FY 1979. The expectation is based on the successful housing of dogs in paddocks during this past severe winter and subsequent plans for developing a second and third paddock.

The goat, miniature swine, and burro breeding herds will continue to expand.

Health surveillance of ungulate herds and flocks will be augmented. Emphasis will be placed on identification of Johne's-positive goats and eliminating them from the herd.

A facility to breed and study the reproduction physiology of New World primate species is to be developed. The inventory of rhesus monkeys in quarantine and contract production will be reduced because of decreased issues.

Improvements to the leased property consisting of some 200 acres of pasture and several buildings adjacent to the Animal Center will continue in anticipation of the property being purchased by NIH. Additional temporary buildings for expansion of the miniature swine herd will be purchased, and a temporary building to house poultry is planned.

2. Comparative Pathology Section

Genetic profiles are being established for the inbred strains of mice produced by VRB. Profiles for 41 strains using 31 markers will be established during the coming year if a full complement of experienced personnel and adequate facilities are available; remodeling will begin soon. Roughly 160 to 320 mice from the foundation colony of each strain will be examined by progeny tests, electrophoresis, immunochemistry, enzymologic and chromatographic procedures. When the animal genetic monitoring program becomes fully operational, consideration will be given to the possibility of monitoring, in limited fashion, the animals provided through contract production.

3. Small Animal Section

The eight-year plan for renovation of the rodent facilities has been modified slightly. The requirement to house large expansion colonies from which to supply production contractors has diminished as a result of collaborative contractural efforts with NCI. The Cancer Institute will begin to provide, DRS with BALB/cAnN, C57BL/6N, DBA/2N, and CDF_1 mice. Immediate effects of this arrangement will be to permit expansion of HSFR and HSFS mouse colonies for the BoB testing program and development of a long-term holding capability for geriatric studies of rats for NCI and the National Institute on Aging. Coupled with the addition of a new room to the barrier, it is expected that nude mouse production can be expanded significantly in the coming year. Renovations of Building 14E will be complete in FY 1978 and will provide research and animal holding space for the Section's professional staff, and an isolation facility for holding contract-produced animals before monitoring procedures.

A management analyses survey of the Section is currently in progress. Results should be helpful in determining current and projected needs for computerized recordkeeping systems as well as in developing better workload indicator and communications systems.

A contract is being developed to provide guidance, through an expert committee, concerning additions to and deletions from the genetic resource. Until then, decisions in this regard will be based on responses of NIH researchers to surveys concerning their needs.

Specifications have been developed for the contract production of hamsters, OM rats, inbred guinea pigs, and NIH and GP mice. It is planned to advertise for contracts in the order listed as soon as the contract with NCI is functioning well. Specifications have also been submitted to obtain animal transportation services by contract instead of purchase order.

Contract specifications will be developed to permit updating the NIH Rodent Catalogue and documentating strain and stock characteristics.

A review of commercially available caging for rabbits and guinea pigs will be completed. Depending on the outcome, a decision will be made to purchase or develop new caging.

4. Veterinary Medicine and Surgery Section

During FY 1978, all three units of this section expect to fulfill increased collaborative and research support activities. Also, each unit will be involved in major renovations or architectural plans preparing for major renovations.

The Surgery Unit renovation and expansion of facilities in Building 14E will acquire the surgical activities of NHLBI currently in Building 3, which will essentially centralize all experimental surgery of large laboratory animals in one facility. The centralization of facilities, equipment, supplies, and support personnel will attract other surgical research in the Bureaus, Institutes and Divisions, which will allow reassignment of these scattered, smaller surgical areas to other research functions.

The Primate Research Unit will continue to expand to meet the needs of investigators in areas of research holding, consultation, collaborative research, primate disease surveillance, and animal models for human diseases.

The Comparative Medicine Unit will expand its role in pre and postoperative care to support the Surgery Unit. Extensive renovations will facilitate studies dependent upon strict environmental controls. The Comparative Medicine Unit has four indoor animal wards, two of which have been renovated, in Building 28. The other two still require renovations during FY 1978. A laboratory is being modified for research diet preparations and bench space for analyses of biological specimens.

The research services provided by this section are unique and vital to all BID intramural programs. Current contract services complement support for each program, but cannot replace the on-campus research activities essential for intramural scientists. The future of those activities is dependent on the proposed new construction of a multilevel centralized laboratory animal facility for the NIH campus.

PROJECT NUMBER (Do NOT use this space)	HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00001-07 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Animal Model Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: C.T. Hansen Geneticist VRB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The program is concerned with developing animal models for biomedical research utilizing the VRB Genetics Resource by following the appropriate mating techniques. One component of the program involves forming, all on the same genetic background, four groups of mice which are defined with respect to T and B lymphocyte activity utilizing two independently occurring mutations; nude (nu) which results in thymic dysgensis and a Z-linked mutation which affects the maturation of B lymphocytes. This system is being introduced into 10 inbred mouse strains. Also, the mutant, motheaten (me) is being introduced into four inbred strains of mice and the gene, Dwarf (dw), into three strains. In the rats, the genes, Corpulent (cp), Diabetes Insipidus (di), and Jaundice (j) are being introduced into two strains.

PHS-6040
(Rev. 10-76)

Objectives: To develop animal models for biomedical research using the VRB Genetic Resource.

Methods Employed: Application of the appropriate mating system in combination with continuous physiological monitoring to yield the desired model.

Major Findings: The major development during the past year has been to undertake a program which should yield a powerful model for those areas of biomedical research having immunology as the primary element. Utilizing two independently occurring mutants in the mouse, one which affects the T lymphocyte and the other the B lymphocyte function, a balanced experimental system is possible. Mating programs have been undertaken to establish this system in some 10 inbred mouse strains. It is expected that a minimum of three to five years will be required to complete this program.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 00002-06 VR

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Development of Diets for Laboratory Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Knapka	Nutritionist	VRB DRS
OTHER:	K.P. Smith	Geneticist	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Veterinary Resources Branch

SECTION

Small Animal Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A laboratory animal nutritional research program is being conducted with various strains and stocks of small animals maintained in conventional and specific pathogen-free environments. The primary objectives of the program are to develop and evaluate open formula rations (open formula=complete list of indredients) that can be used to improve the nutritional status of animal colonies and to identify differences in nutrient requirements among various strains and stocks of animals. A series of factorial-designed feeding trials are conducted to determine the effect of varying concentrations of major and minor nutrients on growth, reproduction, and maintenance of different rat, mouse, guinea pig, and rabbit strains.

PHS-6040
(Rev. 10-76)

Objectives: To improve the nutritional status of NIH production colonies of laboratory animals by identifying the quantitative nutrient requirements of specific stocks and strains of animals and then providing open formula (open formula=complete list of ingredients) rations that contain these nutrient concentrations. To identify possible differences in nutrient requirements between animals maintained in conventional and specific pathogen-free environments. To provide NIH investigators with open formula rations to accommodate specific research projects.

Methods Employed: A series of factorial-designed feeding trials are conducted to determine the effect of varying dietary concentrations of crude protein, crude fat, crude fiber, minerals,and vitamins on growth and reproduction in mice, rats, guinea pigs, and rabbits maintained in conventional and specific pathogen-free environments. Criteria of evaluation include number of pregnancies, number of litters born and weaned, number of pups born and weaned, mortality, weight of offspring weaned, and the postweaning growth of offspring. Studies are also being conducted to determine the digestibility of nutrients in experimental rations. Data from all studies are coded for computer analysis by the appropriate statistical methods.

Major Findings: The evaluation of reproductive data collected from a large number of mouse and rat strains reared under a specific pathogen-free environment have verified experimental data which indicated that the dietary protein concentration for most strains of these rodents can be decreased from 24 to 18 percent without any significant decrease in reproductive performance. These results also show an apparent difference in nutrient requirements between rats and mice and among various stocks and strains within each species.

Results of studies involving rabbits maintained in a specific pathogen-free environment indicate that a high mortality rate occurring in preweaning pups is not affected by changing the source of dietary fiber in the compounds used to provide trace minerals.

Significance: The efficiency of maintaining production and research colonies of laboratory animals can be markedly improved when rations can be developed that supply nutrients in concentrations nearly equal to the requirements of the animal strain involved. Open formula rations formulated for specific research projects, or for standard rations, provide NIH investigators and the scientific community with an essential research tool when experimental data is to be verified by repeating experiments.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00004-16 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Tyzzer's Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.R. Ganaway	Veterinary Microbiologist	VRB DRS
OTHER:	T.H. Spencer	Microbiologist	VRB DRS
	A.M. Allen	Chief, CPS	VRB DRS
	G.L. Clarke	Veterinary Pathologist	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.7	0.7	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The continuing purpose of this project is the study of Tyzzer's disease. The topics of present interest are: (1) characterization of the causative agent, Bacillus piliformis; (2) the serological response of the host to B. piliformis infection using the complement fixation test and fluorescent-antibody techniques; (3) The relationship of isolants from the rabbit and horse foal; (4) the pathogenesis of Tyzzer's disease in a variety of laboratory animals; (5) the stability of the spores of B. piliformis under a variety of conditions including temperature variation and contact with chemical; (6) the epidemiology of Tyzzer's disease, studies with a view toward determining primary sources of infection in nature.

Objectives: To further characterize the etiologic agent of Tyzzer's disease. To study the pathogenesis of the disease through experimental transmission studies. To develop serologic techniques for detection of antibody. To develop means to prevent or control the disease.

Methods Employed: Microbiology, immunology, and pathology

Major Findings: Cottontail rabbits (Sylvilagus floridanus), trapped as juveniles and held in captivity for four years, appear to be the most susceptible to Tyzzer's disease of all animal species tested in the laboratory thus far. Also, results of a serologic study (complement fixation) of sera obtained from cottontail rabbits living in an uncontrolled environment revealed prevalent infection with Bacillus piliformis, the etiologic agent of Tyzzer's disease. The findings pave the way for explaining the extreme cyclic population pattern of cottontail rabbits in the wild and suggest a possible source (spore-contaminated animal feed) of infection for laboratory animals which are cesarean derived and maintained under barrier colony conditions.

Significance: The number of animal species in which Tyzzer's disease is recognized as a cause of fatal disease continues to increase. Within the past year, cottontail rabbits, coyotes, dogs, and guinea pigs have been added to the list, which already includes mice, rats, hamsters, gerbils, laboratory rabbits, wild hares, nonhuman primates, muskrats, cats, and horses. The natural history of the disease remains unknown. The etiologic agent, a gram-negative, spore-forming, obligate intracellular parasite, is unique in the field of microbiology and remains unclassified. This disease occurs throughout the world, causes fatal epizootics in a wide variety of animal species, and is one of the more important diseases of laboratory animals that interferes with and complicates biomedical research.

Proposed Course: Continuation

Publications:

Canaway, J.R., McReynolds, R.S., and Allen, A.M. Tyzzer's Disease in Free-living Cottontail Rabbits (Sylvilagus floridanus) in Maryland. J. Wildlife Dis. 12: 545-549, 1976.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00007-03 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Environmental Toxicosis of Rhesus Monkeys -- Perrine Primate Facility

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G.L. Clarke	Veterinary Pathologist	VRB DRS
OTHER:	A.M. Allen	Chief	VRB DRS
	N. Altman	Senior Investigator	

COOPERATING UNITS (if any)

Perrine Primate Research Center, Perrine, Florida

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective was to determine the cause of progressive debilitation and death of rhesus monkeys housed at contractor's facilities in Perrine, Florida. Many monkeys manifested typical signs and pathological lesions consistent with polychlorinated biphenyl (PCB) intoxication. Tissues from affected animals were analyzed and found to contain toxic levels of PCB's. The source of the PCB appears to be concrete sealer used on the outside runs. The runs were resurfaced with a polyurethane base material and the problem has subsided. The investigation has been terminated.

Objectives: To determine the cause of progressive debilitation and death among the rhesus monkeys housed at the contractor's facilities in Perrine, Florida.

Methods Employed: The problem was studied by histopathological, clinical, pathological, and epidemiological means. The history and pathology suggested toxicosis produced by exposure to polychlorinated biphenyls (PCB). Tissues and materials suspected of containing the compounds were analyzed by gas chromatographic and mass spectrophotometer methods.

Major Findings: See Summary of Work. The project has been terminated.

Proposed Course: Completed

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00008-03 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Neoplasia in the Nude Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G.L. Clarke	Veterinary Pathologist	VRB DRS
OTHER:	C.T. Hansen	Geneticist	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Tumors involving many organ systems have been collected to date. They are being classified histologically. The information is being correlated with nude mouse production figures to determine the incidence of neoplasia in the nude mouse.

Objectives: To determine the prevalence and types of neoplasia that occur in the nude mouse, an inbred strain genetically difficient in cell-mediated immunity.

Methods Employed: Retired females are maintained behind the barrier at Building 14G for aging and sent to the Comparative Pathology Section when they show signs of abnormality. Males are sent to the Section following retirement and are maintained in relative isolation in the Horsfall units and killed when they exhibit abnormal signs.

Major Findings: To date over 30 neoplasms have been collected from nude mice. They are being classified histologically and the results are being prepared for publication.

Significance: Determination whether nude mice have a significant rate of neoplastic disease will be a worthwhile contribution to establishing the relationship between cell mediated immunity and neoplasia.

Proposed Course: The project is being terminated with publication of the data.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00009-04 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Sodium Cyanate Neurotoxicity in Macaca nemastrina primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.K. Johnson	Chief, VMSS	VRB DRS
OTHER:	R.A. Whitney, Jr.	Chief	VRB DRS
	F. Anderson	Chief, MH	IR NHLBI

COOPERATING UNITS (if any)
Molecular Hematology Branch, Division of Intramural Research, NHLBI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.3	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Sodium cyanate, a chemotherapeutic agent for sickle cell disease, inhibits irreversibility of the sickling of erythrocytes from patients with the disease by reacting specifically with the NH_2-terminal valine of the hemaglobin molecule without significantly destroying erythrocyte metabolism of function. We are studying whether sodium cyanate elicits neuropathologic lesions in pigtail monkeys, Macaca nemastrina, as has been suggested. The outcome of this study will provide information for development of clinical studies of human beings with sickle cell disease.

Methods Employed: Twenty adult female pigtail monkeys, (Macaca nemastrina, were divided into four groups; one serves as a control and the other three groups receive daily subcutaneous injections of sodium cyanate of 40 mg/kg, 25 mg/kg, and 15 mg/kg, respectively. Selected animals are humanely killed and perfused for neuropathological examination. Clinical neurological examination and clinical laboratory tests are conducted during the course of the experiment. Baseline hematology, clinical chemistries, and neurological evaluation have been compiled over a three-month stabilization period.

Major Findings: The 25 mg/kg dose and 35 mg/kg dose of sodium cyanate in pig-tailed monkeys produced mild clinical neuropathies and other general toxic effects such as depression and intermittent anorexia. The animals receiving 15 mg/kg remained clinically normal. Histopathology of the cerebrum, cerebellum and brain stem failed to show abnormalities. Sections throughout the spinal cord revealed swelling and demyelination in the pyramidal tracts both crossed and uncrossed. Sections from the roots and peripheral nerves showed no abnormalities except for an occasional swollen axon.

Significance: Sodium cyanate reverses the sickling of erythrocytes and results in relief of symptoms of sickle cell disease without impairing the oxygen transport system of erythrocytes. Establishing a dose-toxic curve in primates will lead to implementation of safe clinical dosage curves for human beings with the disease. Sodium cyanate is of interest for in vivo clinical use as well as extracorporeal treatment of affected erythrocytes. The drug has potential for other anemias associated with abnormal hemoglobin caused by genetic, inborn errors of metabolism.

Proposed Course: Compare short-term and long-term effects of sodium cyanate on the peripheral and central nervous system. Short-term effects have been identified; investigation of long-term effects is continuing.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 00010-04 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Erythrocebus patas Monkey as an Animal Model for Cardiovascular Research

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.L. Fry	Chief, EA	IR NHLBI
OTHER:	R.W. Mahley	Chief, CAAMS	IR NHLBI
	D.K. Johnson	Chief, VMSS	VRB DRS

COOPERATING UNITS (if any)

Laboratory of Experimental Atherosclerosis, NHLBI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	1.0	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

To determine the advantages of the patas monkey for studies designed to lead to information concerning atherosclerosis in human beings.

PHS-6040

Methods Employed: Fifty patas monkeys (Erythrocebus patas) were purchased and maintained on monkey chow for four months while baseline data was obtained. They were randomly divided with equal sex distribution into one group of 10 animals receiving monkey chow, one group of 20 receiving meals high in fat and low in cholesterol, and one group of 20 receiving meals high in both fat and cholesterol. Monthly blood samples were drawn and hematological, serum chemistries, and serum lipid profiles were obtained.

Major Findings: Total serum cholesterol levels were significantly high in the group fed the diet high in both fat and cholesterol. The group fed the diet high in fat and low in cholesterol and the control group maintained normal levels of total serum cholesterol. No significant differences were found between males and females of each group. A rapid rise occurred in arginine-rich lipoproteins in the high-cholesterol group. A low-density lipoprotein in the patas monkey cross-reacted immunologically with low-density lipoprotein from a human being. The patas may serve as an interesting model for lipoprotein research. Gross and histopathologic lesions were similar to naturally occurring atherosclerotic lesions in human beings.

Significance: Atherosclerosis is a leading cause of death. Our studies may elucidate the pathogenesis of the disease and provide answers concerning its control. The patas monkey is emerging as one of the best primate models for the disease in human beings.

Proposed Course: Continuation. A new group of patas monkeys are undergoing baseline evaluation to study further lipoprotein-related biochemical factors.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00011-03 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Effect of Season on Pituitary and Gnodal Hormone Levels in Adult Male Macaques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.K. Johnson	Chief	VRB DRS
OTHER:	G.D. Hodgen	Chief	RR NICHHD

COOPERATING UNITS (if any)

Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.25	0.25	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this study is to assess the seasonal changes in endocrine parameters important in male fertility. Measurements of androgens measured as a biorhythm will be correlated to breeding efficiency and season.

PHS-6040
(Rev. 10-76)

Methods Employed: Ten male breeder monkeys were bled the first five days of each month for a 12-month period. Follicle stimulating hormone, luteinizing hormone, testosterone, and androsterone were assayed using sensitive radio-immunoassay methods. The results were correlated with time of month, season, and breeding efficiency.

Major Finding: Animal study is completed and radioisotope analyses of serum hormones are being accomplished.

Significance: Fertility and sterility studies focusing on male endocrine parameters have not been extensive. Approaching male endocrine changes as a biorhythm may lead to basic understanding of reproductive endocrinology. In addition, our results may may be applied directly to biomedical research to improve nonhuman primate breeding, which is important because large-scale domestic colonies are a major resource to the scientific community.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00012-03 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)
Hormone Level During the Postpartum Interval in Nursing and Non-nursing Macaques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.K. Johnson	Chief	VRB DRS
OTHER:	G.D. Hodgen	Chief	RR NICHD

COOPERATING UNITS (if any)

Section on Endocrinology, Reproduction Research Branch, NICHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	0.5	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The interval between delivery and the first fertile menstrual cycle in rhesus monkeys is not known. Breeding management requires such information to maximize the use of breeder males, which allows efficient space management and timed mating. Serum levels of various gonadal hormones will be measured to identify the onset of ovulating menstrual cycles.

Methods Employed: Five nursing rhesus monkey mothers and five non-nursing mothers were bled on 90 days beginning one day after delivery. Serum levels of follicle stimulating hormone, luteinizing hormone, estradiol, estrone, and progesterone will be measured to identify the onset of ovulatory menstrual cycles.

Major Findings: Animal aspects of the study are completed and analyses of the serum hormones are in progress.

Significance: Development of domestic breeding colonies of rhesus monkeys for biomedical research requires better understanding of their reproductive physiology and improved fertility and management practices. Our findings may also provide endocrine parameters applicable to study of various conditions in human beings.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00013-03 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Mycoplasma-Induced Caprine Keratoconjunctivitis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.J. BAAS	Head, CU	VRB DRS
OTHER:	M.F. Barile	Director, MB	DBP BOB
	R.M. Franklin	Ophthalmology Resident Johns Hopkins University	

COOPERATING UNITS (if any)
Bureau of Biologics, Food and Drug Administration
Wilmar Ophthalmology Institute, Johns Hopkins Univ., Baltimore, Maryland

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective is to determine if Mycoplasma conjunctivae is an etiological agent of naturally occurring caprine keratoconjunctivitis (pinkeye). Attempts are being made to experimentally induce the disease and study both forms by bacteriological, serological, pathological, and serum chemistry methods.

PHS-6040
(Rev. 10-76)

Objective: The objective is to determine if Mycoplasma can cause keratoconjunctivitis by studying natural and experimentally induced disease.

Methods Employed: Mycoplasma culturing of lacrimanl fluids, joint fluid, and blood; metabolic inhibition tests and lymphocyte transformation tests to measure the immune response; blood studies including complete blood counts, protein electrophoresis and some serum chemistries.

Major Findings: Protective immunity may require prior eye infection and/or systemic infection. Induced eye disease was similar to the natural disease.

Significance: Another Mycoplasma has been found to cause eye disease in conjunction with concurrent respiratory disease and arthritic condition, which may also occur in Reider's syndrome of humans. The significant findings contribute to the understanding of periodic episodes of eye disease in the Animal Center goat herd.

Proposed Course: This project has been completed and a manuscript has been submitted for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00014-03 VR

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Evaluation of Efficacy of M. bovis PPD Tuberculin in the Detection of Tuberculosis in Wild Caught Indian Macaca mulatta Monkeys

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.M. Renquist	Head, PQU	VRB DRS
OTHERS:	M.L. Morin	Veterinarian	VRB DRS
	D.W. Johnson	Univeristy of Minnesota	
	L. Conyha	Staff Veterinarian	
	C. Thoen	Head, Mycobacteriology	USDA

COOPERATING UNITS (if any)

Veterinary Services Laboratories, Mycobacteriology Section, APHIS, USDA, Ames, Iowa 50010

Dept. of Veterinary Clinical Science, Univ. of Minnesota, St. Paul, Minnesota

LAB/BRANCH

Veterinary Resources Branch

SECTION

Animal Center Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study will provide data to determine the efficacy of M. bovis PPD Tuberculin for the early detection of tuberculosis when and if mammalian tuberculin (OT) is no longer available. Additionally, through the use of clinical pathologic and immunologic tests and the use of equivalent PPD or OT concentrations, various parameters such as erythrocyte sedimentation, lipoproteins, lymphocyte transformation, and skin testing can be efficiently and effectively evaluated.

PHS-6040
(Rev. 10-76)

Objectives: Suitable and reliable methods of tuberculin testing in nonhuman primates have evolved utilizing commercially prepared USDA mammalian tuberculin. Early detection of tuberculosis is essential, and reliability on a constant supply of commercially prepared mammalian tuberculin is mandatory. This study will provide data to determine the efficacy of M. bovis PPD tuberculin (the concentrated primate material 130,000 TV's per ml and the cattle testing material 15,000 IV's per ml) for the early detection of tuberculosis when and if mammalian tuberculin (OT) is no longer available. Through the use of clinical, pathologic, and immunologic tests such as skin testing with equivalent amounts of PPD and OT, erythrocyte sedimentation (ESR), lipoproteins, lymphocyte transformation (LT), and a full clinical path profile, various parameters can be efficiently and effectively evaluated.

Methods Employed: Standard tuberculin testing procedures will be maintained to detect reactor animals; i.e., 0.1 ml Jensen-Salisbury mammalian OT (full strength) administered intradermally in alternate eyelids at two-week intervals. Comparison of mammalian and Old Tuberculin full-strength and PPD will be made in several groups of reactors. Reactors will also be caged with healthy animals and these healthy cage mates will be tested at weekly intervals for conversion.

Major Findings: Twenty-five rhesus monkeys, including spontaneous reactors and normal cage mates, have been utilized in the study. Reactors: (1) Full-strength mammalian tuberculin vs 1/10 mammalian tuberculin. The FS tuberculin stimulated a greater reaction than tuberculin diluted one part in ten; the reaction was two to three times greater, in size and intensity, as measured by erythemia and skin thickness ratios.

Mammalian vs equal concentrations of Mycobacterium bovis-derived PPD: The mammalian tuberculin reacted with the same intensity and duration as the PPD. Regardless of concentrations used, both reactions subsided at the same time in animals becoming anergic. The only difference was that the "erythemia" with PPD was a yellowish color in certain instances, making observation difficult; however, the size difference was not significant. The strongest concentration of PPD available is 2 mg of protein, which is equivalent to 1:1.5 diluted mammalian tuberculin. Based on observations in the previous paragraph, full-strength undiluted mammalian tuberculin will give a stronger reaction than 1:1.5 tuberculin or 2 mg protein PPD. All the reactors to date have been confirmed as having Mycobacterium bovis as the etiologic agent. Results cannot be compared of M. tuberculosis using M. bovis PPD.

Lymphocyte transformation testing: The results have not been correlated, however, preliminary information indicates that the tuberculin testing interferes with the lymphocyte stimulation. Whether this dose is related is uncertain. A revised protocol should resolve this difficulty.

Other clinical parameters: The findings to date indicate the erythrocyte sedimentation rate was increased in all reactors throughout the study, increasing to 22 mm/hour in one case. Other clinical pathologic parameters are being studied.

Conditioned cage mates: The difficulty is in being able to infect the cage mate. To date no cage mate has become infected with tuberculosis, despite periods of up to three months contact with tuberculosis reactors showing extensive lesions. Until this problem is resolved the question of PPD versus tuberculin and initial reaction time cannot be answered.

Significance: The variability in immune response to PPD or OT with natural cases of primate tuberculosis will be determined. Better understanding in the use of PPD or OT and their efficacy will be valuable in early detection of tuberculosis in research and quarantine colonies of nonhuman primates.

Proposed Course: Indefinite

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 00015-03 VR

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Defining the Nude Mouse Model

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.A. Whitney, Jr.	Chief	VRB DRS
OTHER:	C.T. Hansen	Geneticist	VRB DRS
	J.R. Ganaway	Veterinary Microbiologist	VRB DRS
	A.M. Allen	Chief, CPS	VRB DRS
	C.K. Hsu	Ft. Detrick, Maryland	FCRC
	H.J. Alter	Blood Bank	CC
	P. Holland	Blood Bank	CC
	R. Purcell		LID NIAID

COOPERATING UNITS (if any)

Laboratory of Infectious Diseases, NIAID
Blood Bank, Clinical Center
Dept. Laboratory Animal Medicine, Johns Hopkins Univ., Baltimore, Maryland

LAB/BRANCH

Veterinary Resources Branch

SECTION

N/A

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 2001.

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keyword)

A congenic strain of mouse crossed with CBA inbred will be used to again attempt to identify an animal model for human hepatitis A and B. This congenic strain CBA/nude will lack the thymus and T system of the nude and also lack some elements of the B immune system inherent in the CBA mouse.

PHS-6040
(Rev. 10-76)

Objectives: To determine the susceptibility of the nude, athymic mouse to viral, parasitic, and bacterial diseases, and to define the role of the thymus activated "T" lymphocytes in susceptibility and the pathogenesis of infectious diseases.

Methods Employed: Weanling nude mice are transferred directly from the Building 14G barrier to presterilized, germfree isolators. Protecing this highly susceptible animal from the conventional environment with the flexible plastic isolator system has proven extremely successful. Most nudes, who have a 4-month life span in conventional animal quarters, survived until sacrificed at 22 months in our isolator system.

This project originated as an attempt to infect nude mice with human hepatitis A and hepatitis B. Sera from a human known to be infected with "B " and from a chimpanzee known to be infected with "A" were injected intravenously into separate groups of animals.

Major Findings: This project is an attempt to further define the role of the nude, athymic mouse as a model for various human disease processes. Initial exposure to the nude mice with human hepatis A and B virus was unsuccessful. A group was also infected with schistosomiasis. They demonstrated the role of the cellular immune response in lesions of schistosomiasis. The breeding of the nude as a congenic with inbred strains of mice lacking specific immune responses will be continued in an effort to provide new models for human infectious diseases.

Significance: The congenital, athymic state, withits resulting lack of cell-mediated immunity in the nude mouse, may be one of the most significant events in the search for animal models for diseases of humans. It must continue to be better defined in a number of areas to realize its potential in biomedical research.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00016-02 VR

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Characterization of a New Viral Disease of Rabbits

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.D. Small	Animal Disease Investigator	VRB DRS
OTHER:	R.A. Squire	Pathologist, Johns Hopkins University	
	L. Aurelian	Virologist, Johns Hopkins University	
	J.D. Strandberg	Pathologist, Johns Hopkins University	

COOPERATING UNITS (if any)

Johns Hopkins University School of Medicine, Baltimore, Maryland

LAB/BRANCH

Veterinary Resources Branch

SECTION

Small Animal Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(Es)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The goal of this project is to isolate and characterize the agent that causes a disease recently recognized in rabbits, describe the clinical course, define the lesions, study the mode of transmission, and define the host range. Work so far indicates the agent is a virus. The target tissue is muscle, and the only known susceptible host is the rabbit.

PHS-6040
(Rev. 10-76)

Objectives: To characterize the etiological agent of a hitherto undescribed disease. To study the pathogenesis of the disease.

Methods Employed: Microbiology, immunology, and pathology

Major Findings: The disease is caused by a coronavirus. It is highly infectious for the rabbit by inoculation but has not yet been naturally transmitted between rabbits. Other species have not been infected. A specific myopathy is associated with the disease.

Significance: Identification of the causal agent may prove useful in the study of myocardial degenerative disease as it appears to have an affinity for myocardial tissue.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00017-01 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Experimental Atherosclerosis in Miniature Swine

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.W. Mahley	Chief, CAAMS	IR NHLBI
OTHERS:	D.L. Fry	Chief, EA	IR NHLBI
	R.L. Killens	Head, CMU	VRB DRS
	D.K. Johnson	Chief	VRB DRS
	J.J. Knapka	Nutritionist	VRB DRS
	R.M. Jaffe	Physician	CP CC

COOPERATING UNITS (if any)
Laboratory of Experimental Atherosclerosis, NHLBI
Clinical Pathology Department, Clinical Center

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	2.0	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

To determine the effects of different kinds of dietary fats with and without cholesterol on the pathogenesis of atherosclerosis, using miniature swine as an animal model for the disease in human beings. Experimental atherosclerosis in miniature swine provides a model system for studying the interrelationships of dietary and biochemical factors germane to the basic causes and mechanism of atherosclerosis.

PHS-6040
(Rev. 10-76)

Methods Employed: Fifty miniature swine were obtained from an established biomedical research center. The animals were of uniform age and size with an equal sex distribution. Following baseline blood chemistry profiles, the animals were divided into groups receiving the following dietary supplements: tallow, tallow with 1.5 percent cholesterol, tallow with 1.5 percent cholesterol plus 0.75 percent taurocholic acid; lard, lard with 1.5 percent cholesterol, lard with 1.5 percent cholesterol plus 0.75 percent taurocholic acid; cottonseed oil, cottonseed oil with 0.5 percent cholesterol. The swine were kept on the diets for six to twelve months. Blood chemistry was studied and weight determined biweekly. Monthly serum samples were collected for isolation and measurement of specific lipoproteins.

Major Findings: Total serum cholesterol levels in pigs fed cholesterol diets rose 400 mg percent above baseline values during the first four months of the study and then decreased to 250-300 mg percent above baseline levels. This rise and fall of total serum cholesterol level is characteristic in swine and may be related to lipid metabolism, cholesterol transport systems, or other enzymatic factors in swine. Both high and low levels of serum cholesterol have been found in animals receiving tallow with 1.5 percent cholesterol. Platelet cell kinetic studies suggest differences between the groups and may correlate to the genesis of the disease. Necropsy of pigs on the diet for six months revealed gross aortic lesions similar to those seen in human beings with atherosclerosis. Histologic study showed raised fibrous plaques with infiltration of lipoproteins into the intima, cholesterol clefts, necrosis, and encroachment of the basement membrane. Thrombosis of the coronary and basilar arteries were found in pigs fed the high cholesterol diets.

Significance: Detailed investigation of induced atherosclerosis in animal models such as miniature swine is needed to explore the underlying causes and progression of the disease. Atherosclerosis is a major disease of human beings, a leading cause of death, and a debilitating disease affecting people of all ages. The ability to produce the disease in a reliable, reproductive manner will permit study of a variety of parameters.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00018-02 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

The Pathogenesis of Chondrodysplasia in the Alaskan Malamute

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.M. Young	Acting Head, PS	LT NCI
OTHERS:	R.L. Killens	Head, CMU	VRB NCI
	J.M. Ward	Veterinary Pathologist	LT NCI
	D. Prieur	Pathologist	LT NCI

COOPERATING UNITS (if any)

Laboratory of Toxicology, National Cancer Institute

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Alaskan malamute has naturally occurring chondrodysplasia, an inborn error of metabolism that appears as a recessive trait with varying degrees of expression. The animal serves as a useful model for studying the pathogenesis of chondrodysplasia. Observation of growth patterns in puppies is especially useful. Studies of biochemical, histochemical, and morphological changes serve to define the disease in human beings. They may also elucidate mechanisms of pathogenic processes that occur with neoplasms of the skeletal system.

PHS-6040
(Rev. 10-76)

Method Employed: A small colony of ten Alaskan malamutes has been acquired. A high incidence of chondrodysplasia occurs in the offspring. The dogs are mated and all offspring are radiographed at established intervals to detect early change and growth patterns indicative of chondrodysplasia. Currently, the main emphasis is on repeated breeding and evaluation of bitches and studs to obtain an increased number of puppies with the defect.

Major Findings: It was observed that conception rates were lower during the summer months and litters born during the summer months were smaller. However, puppies have been produced with chondrodysplasia. The growth patterns of long bones and epiphyseal development closely resemble the morphological dysplasia seen in people with the abnormality.

Significance: Cellular changes in cartilage and bone that accompany chondrodysplasia can be studied in the Alaskan malamute. Identification of morphological and biochemical alterations in animals with the disease elucidate cellular defects that occur with other diseases that affect bone and cartilage such as osteosarcoma.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00019-01 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Aging Studies on HSR, HSR-Stroke Prone, WKY Rats

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G.L. Clarke	Veterinary Pathologist	VRB DRS
OTHER:	D. Goodman	Veterinary Pathologist	EXP NCI
	S. Potkay	Chief, SAS	VRB DRS
	C. Hansen	Geneticist	VRB DRS

COOPERATING UNITS (if any)

Experimental Pathology Branch, NCI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.2	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective is to determine the nature and incidence of pathologic lesions that develop throughout the lifespan of HSR, HSR-stroke prone, and WKY rats. In each strain, 100 animals of both sexes will be selected for long-term holding. Some subjects will be killed at the following ages: 2 months, 8 months, 18 months 15 months, 18 months, 21 months, and 28 months. Tissues will be studied by light microscopic methods and, if indicated, electron microscopic techniques. These strains have great potential as animal models for the study of cerebrovascular and hypertensive disease in human beings. Their value depends on accurate pathological description and documentation.

PHS-6040
(Rev. 10-76)

Objectives: To determine the nature and incidence of pathologic lesions that develop throughout the lifespan of HSR, HSR-stroke prone, and WKY rats. HSR rats are reported to be hypertensive, +140 mm Hg, but study of the strain apparently has not been made. The HSR-stroke prone rat is reported to spontaneously develop cerebral infarcts, although documentation is sketchy. The WKY is the parent strain of the HSR and HSR-stroke prone rat and will be studied as a control.

Methods Employed: One hundred animals of each sex/strain will be selected for long-term holding. Some subjects will be killed at the following ages: 2 months, 8 months, 12 months, 15 months, 18 months, 21 months, 24 months, and 28 months. Tissues will be studied by light microscopic methods and, if indicated, electron microscopic techniques.

Significance: These strains have great potential as animal models for the study of cerebrovascular and hypertensive disease in humans. Their value depends on accurate pathological description and documentation and will have been established if correlation between the disease in the animals and human beings is good.

Proposed Course: Animals will be selected and studied this year.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00020-01 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)
In utero Injection of Herpes saimiri, Epstein-Barr Virus, or Guinea Pig-like Herpes virus in Pregnant Guinea Pigs

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.W. Pearson	Head, IS	VI NCI
	J.D. Bacher	Head, SU	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Branch

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective is to see if oncogenic viruses injected in utero in fetuses will produce death or tumors.

PHS-6040
(Rev. 10-76)

Methods Employed: Fifteen pregnant guinea pigs (20 to 40 days gestation) will be injected in utero with either Herpes saimiri, Epstein-Barr virus, or guinea pig-like Herpes virus. Three pregnant rabbits will also be injected in utero with either Herpes saimiri or Epstein-Barr virus.

Significance: Guinea pigs are immunologically competent at birth and do not develop tumors when inoculated with oncogenic viruses. They also show a very low incidence of naturally occurring tumors. It is thought that tumors can be produced in guinea pigs by injecting the oncogenic viruses in utero. This would make an ideal animal model for the study of these oncogenic viruses as the guinea pig is easy to handle, will tolerate anesthesia, and is of small size.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00021-01 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Evaluation of Therapeutic Effects of Iron-Dextran, Vitamin B_{12}, and Folic Acid in Combating Experimentally Induced Anemia in Rhesus Monkey (Macaca mulatta)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.K. Johnson	Chief	VRB DRS
OTHER:	G.B. Reddy	Research Veterinarian	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	0.6	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

One of the main aims of this study was to establish the guidelines for how much blood can safely be drawn from a monkey. Information available suggests that 10 percent by weight amount is a safe limit. By using therapeutic agents like iron-dextran, this study establishes that when the dosage is 60 mg/week, 20 percent of blood volume can be safely collected. Another important goal was to determine the therapeutic effect of vitamins and iron-dextran in combating experimentally induced anemia.

PHS-6040
(Rev. 10-76)

Methods Employed: Fifteen female rhesus monkeys were divided into three groups of five each and maintained on monkey chow ad libidum. Baseline blood values for total RBC, WBC, Hct, Hemoglobin, reticulocytes, vitamin B_{12}, and folic acid were established on three consecutive samples. One group of five monkeys received 60-mg injections of iron-dextran weekly, and the second group received B complex vitamins (100 micrograms B_{12}) and 1 microgram folic acid daily by intramuscular injection; the third group did not receive any treatment. In the first phase, a total of 10 percent blood volume was collected three days a week for five weeks. In the second phase 20 percent blood volume was collected three days a week for up to nine weeks. Blood sampling was discontinued when hematocrit and hemoglobin values fell below 50 percent of the base values, and complete blood counts were taken three times a week to follow the reestablishment of base level hematological values. Injections of iron-dextran and vitamins were continued even when blood sampling was discontinued. On all the samples, total red cells, white cells, reticulocytes, hematocrit, hemoglobin, vitamin B_{12} and folic acid were determined.

Major Findings: Monkeys treated with 60 mg iron-dextran per week did not show any ill effects, even though 20 percent of their blood volume was taken for six to eight weeks. In the controls and the vitamin-treated group, values fell generally below 50 percent baseline values in three to six weeks. However, values for two monkeys in the control group did not drop below 50 percent base levels after being bled for nine weeks.

Significance: The iron-dextran therapy would be a valuable tool to maintain hemostasis. It would be useful to demonstrate that a maximum of 20 percent blood volume per week can be safely collected from monkeys receiving iron-dextran.

Proposed Course: Study completed

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00022-01 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Skeletal Age Development in Macacca mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Michejda	Comparative Anatomist	VRB DRS
OTHER:	W. Watson	Head, PRU	VRB DRS
	R.L. Killens	Head, CMU	VRB DRS
	J.D. Bacher	Head, SU	VRB DRS
	N.R. Hayes	Deputy Chief	VRB DRS
	D.K. Johnson	Chief	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The most widely used methods (dental age, body weight) for age estimation in nonhuman primates are inadequate. More precise standards and age indicators can be obtained by measuring skeletal age, which has proven to be the best criteria in the assessment of unknown chronological age. Our longitudinal radiographic studies have been undertaken to provide information on the development and bone maturation of the hand and wrist in Macaca mulatta monkeys. Our data will cover the whole period of appendicular bone maturation from 120 days of gestation (the onset of carpal center ossification) to adulthood (over 5 years). To obtain the fetal data, a novel surgical technique of multiple uterontomies was developed. Serial radiographic data is obtained by three uterotomies and after normal delivery. Our radiographic study will provide pre- and postnatal age indicators and will be prepared for publication as an atlas, which should make the data readily usable in many studies where the precise age of the experimental animal is required.

PHS-6040
(Rev. 10-76)

Methods Employed: During the first year of our study, 20 young adult, timed-pregnant Macaca mulatta were used. The first uterotomy was performed on females at 120 days of gestation (approximately 160 mm crown rump lengths) when the onset of wrist ossification corresponding to a newborn child is observed. The left hand of the fetus was exposed and x-rayed. The uniform dorso palmar projection was applied at a constant 40 cm tube to target distance. The x-ray cassettes with intensifying Du Pont screens were used to reduce the exposure time to minimum (1/30 sec., 40 KV, 300 mA). Uterotomies were repeated on days 120, 134, 148 of gestation. Longitudinal radiographic data were obtained during three consecutive uterotomies (2-week intervals) and after delivery. Each radiogram was analyzed and the onset and present of the ossification centers in the wrist and hand were studied. The prenatal data will be incorporated with existing longitudinal postnatal data. Complete information about all stages of bone maturation and development of the hand and wrist of M. mulatta will be evaluated in five age groups: prenatal, neonatal, infant, juvenile, and adult.

Major Findings: The longitudinal radiographic data show no radiographic signs of carpal ossification centers before 120 days of gestation. However, rapid development of the carpal bones in the second trimester of fetal life in rhesus monkeys (between 120-134-148 days of gestation) was observed. Our data indicate that radiograms made every two weeks do not record the rapid changes well enough. It seems that weekly intervals between x-rays are necessary to provide data on hand and wrist development and a complete record of age indicators for the fetus in the second trimester. One conclusion is that the development of the wrist is much more rapid than had been anticipated; sexual dimorphism is less significant during fetal life than had been expected. The surgical technique of multiple uterotomies was improved to such a degree that no fetuses were lost due to stillbirths or premature deliveries. It is believed that this technique may be used in many other aspects of prenatal studies.

Significance: The assessment of bone maturation by use of roentgenograms of the extremities is the best method for determining age. It provides age estimates throughout the developmental period and allows the detection of experimentally induced variations in skeletal development.

Our data obtained from apparently normal fetuses will be valuable for a variety of studies. However, the most important impact of it might be on experimental teratology and genetics, where rhesus monkeys of unknown age are widely used as animal models. Moreover, it should result in an important contribution to better understanding of prenatal development in Macaca mulatta. The data also may serve as a basis for comparison with human material in a variety of studies. Also, the success of the multiple uterotomies may provide new possibilities for prenatal treatment of the human fetus, as for blood disorders when prenatal transfusion is needed but existing methods are risky, for skeletal disorders when early surgical treatment may be of great value and, perhaps, many other disorders that might advisably be corrected by a surgical procedure before birth.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00023-01 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Nonhuman Primate Dietary Fiber Level Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.L. Morin	Veterinarian	VRB DRS
OTHER:	D.M. Renquist	Head, PQU	VRB DRS
	J.J. Knapka	Nutritionist	VRB DRS
	F.J. Judge	Chief	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to determine the optimal level of crude fiber in the diet of feral Asian monkeys, Macaca mulatta, during the quarantine period. The results, thus far, indicate that the standard 3 percent crude fiber level in commercially available laboratory nonhuman primate diets is not the optimal level. It appears that a higher level of crude fiber in the diet of feral monkeys, Macaca mulatta, reduces the number of treatment days for enteric disorders, improves stool characteristics, and does not adversely affect weight gain during the quarantine period.

PHS-6040
(Rev. 10-76)

Objectives: The objective is to determine the optimal level of crude fiber in the diet of feral Asian monkeys, Macaca mulatta, during the quarantine period.

Methods Employed: The monkeys were divided into four groups by a random method. The four diet groups included two 3 percent crude fiber diets, 6 percent crude fiber diet, and a 9 percent crude fiber diet. All diets were balanced for amino acids, fat, ash, minerals, and vitamins.

Major Findings: The number of monkeys that required medical treatments for intestinal disorders was reduced by feeding a 6 percent crude fiber diet. The number of treatment days required to eliminate the intestinal disorders was reduced by feeding the 6 percent or 9 percent crude fiber diets. The 6 percent crude fiber diet improves stool characteristics and does not adversely affect weight gain.

Significance: The 6 percent crude fiber diet improves our ability to maintain the health of wild caught monkeys during the quarantine period. This diet facilitates the transition of these monkeys from the wild to the laboratory environment in the most humane manner.

Proposed Course: Project complete--report is being written.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00024-01 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)
Anthelmintic Affect on Antibody Levels Following Primary and Secondary Immune Stimulation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.L. Morin	Veterinarian	VRB DRS
OTHERS:	G.D. Hodgen	Chief	RR NICHHD
	L.D. Stuart	Head, UU	VRB DRS
	F.J. Judge	Chief	VRB DRS

COOPERATING UNITS (if any)
Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to determine if anthelminthics (Thiabendazole or Levamosole hydrochloride) interface with the normal immune response. Sheep receiving primary or secondary immune stimulation will be routinely wormed and the circulating antibody responses recorded.

PHS-6040
(Rev. 10-76)

Objectives: The objective is to determine if anthelmintics (thiobendazole and levamosole hydrochloride) interfere with the normal immune response circulating antibody levels.

Methods Employed: Sheep receiving primary or secondary immune stimulation were routinely wormed and the circulating antibody responses recorded. Sheep were separated into three groups, one for each anthelmintic and one for saline control.

Major Findings: The results have not been analyzed completely yet. Preliminary information suggests that the drugs do not affect circulating antibody levels.

Significance: The results of the study would seem to indicate that routine worming practices do not affect the immunologic response of antibody-producing ruminants.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00025-01 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Evaluation of a Purified Diet for Rodents

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J.J. Knapka Nutritionist VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	.025	.075

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A feeding trial of being conducted comparing the lifetime performance of noninbred mice fed a standard cereal-based diet and a purified diet formulated with 50 percent glucose. The performance of two generations is being evaluated for differences in growth, reproduction, and lesions associated with aging.

PHS-6040
(Rev. 10-76)

Objectives: To develop a purified diet for laboratory mice that will meet all the nutrient requirements of this species and to test the validity of feeding a diet containing high levels of low-molecular weight carbohydrates to mice for their entire lifespan.

Methods Employed: The feeding trial is designed to compare the performance of two generations of mice fed the test purified diet and a standard cereal-based diet. Criteria of evaluation include number of pregnancies, number of litters born and weaned, number of pups born and weaned, mortality, weight of offspring weaned, postweaning growth of offspring, total days of life, and the onset and distribution of lesions associated with aging. All data are being analyzed by appropriate statistical procedures.

Major Findings: A purified diet has been formulated that will support growth and reproduction in mice comparable to that in mice fed a standard cereal-based diet.

Significance: With the increased interest in the research community for establishing standard procedures covering long-term animal studies, it is essential that data be available regarding the effect of various kinds of diets on lifetime studies of rodents.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00026-01 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Establishment of a Pasteurella multocida-free colony by the use of chemotherapy and mass air movement.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.D. Small	Animal Disease Investigator	VRB DRS
OTHER:	T.D. Moore	Senior Scientist	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The object of this project was to determine if Pasteurella multocida-free rabbits could be raised in an infected colony by use of antibiotics. Infected females given tetracycline HCl in the drinking water during pregnancy and the nursing period consistently produced and raised rabbits free of Pasteurella multocida.

PHS-6040
(Rev. 10-76)

Objectives: To obtain rabbits free of infection with Pasterurlla multocida without the use of surgical procedures.

Methods Employed: Microbiology and pathology

Major Findings: The continuous administration of antibiotics during pregnancy and the nursing period was successful in keeping offspring from becoming infected with Pasteurella multocida.

Significance: The technique provides a simple nonsurgical method for obtaining Pasteurella multocida-free rabbits for use as breeding stock and as experimental subjects.

Proposed Course: Work has been terminated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00028-01 VR

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Effect of DDVP on Reproductive Performance, Weight Gain, and Immunologic Function in Four Strains of Mice

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.D. Small	Animal Disease Investigator	VRB DRS
OTHER:	P.J. Baker	Senior Research Scientist	LMI NIAID

COOPERATING UNITS (if any)

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The object of this study is to determine if the use of dichlorvos (DDVP) pellets in rodent bedding for the control of ectoparasites affects reproductive performance, weight gain, or immunologic function in mice. No effect on immunologic function has been demonstrated. Reproductive performance and weight gain data are currently being measured.

PHS-6040
(Rev. 10-76)

Objective: To determine if dichlorvos (DDVP) pellets in the bedding of mice for ectoparasite control adversely affects reproductive performance, weight gain, or immunologic function.

Methods Employed: Plaque-forming cell assay with sheep red blood cells or pneumopolysaccharide as the antigen.

Major Findings: No adverse effects were demonstrated.

Significance: Based on our findings, DDVP can be safely used in laboratory mice to control ectoparasites.

Proposed Course: Completed

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00028-01 VR

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Effect of Piperazine on T cell and B cell Function in Mice

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.D. Small	Animal Disease Investigator	VRB DRS
OTHER:	P.J. Baker	Senior Research Scientist	IMI NIAID

COOPERATING UNITS (if any)

None

LAB/BRANCH

Veterinary Resources Branch

SECTION

Small Animal Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The object of this study is to determine if the administration of piperazine for the control of pinworms affects immunologic function function in mice. The study is completed and no effect on B cell of T cell function was found using pneumopolysaccharide III as the B cell stimulant and sheep red blood cells as the T cell stimulant. Piperazine .2HCl was given in tap water for three weeks at a dose of 4 or 8 gm/L to BALB/cAnN and 4 gm/L to C57BL/6N, C3H/HeN, DBA/2N, and N:NIH(S) mice without observable changes in immune function.

PHS-6040
(Rev. 10-76)

Objective: To determine if therapeutic doses of piperazine given to mice interfere with T cell and B cell function.

Methods Employed: Plaque-forming cell assay with sheep red blood cells or pneumopolysaccharide as the antigen.

Major Findings: No effect on T cell or B cell function was demonstrated.

Significance: Based on our findings, piperazine can be safely used to treat mice for injection with pinworms in a research colony.

Proposed Course: Completed

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